GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION
SPONSORED PROJECT INITIATION

Date: 1/9/79

Project Title: Synthetic Studies on Sesquiterpenoids

Project No: G-33-642

Project Director: Dr. Drury S. Caine

Sponsor: National Science Foundation, Washington, D. C. 20550

Agreement Period: From 12/1/78 Until ~~80~~ 81*
*Includes 6 month flexibility period

Type Agreement: Grant No. CHE78-10044

Amount: $23,400 NSF Funds (G-33-642)
9,457 GIT Contribution (G-33-334)
$32,857 Total

Reports Required: Annual Progress Reports; Final Project Report

Sponsor Contact Person (s):

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Defense Priority Rating: n/a

Assigned to: Chemistry (School/Laboratory)

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GEORGIA INSTITUTE OF TECHNOLOGY OFFICE OF CONTRACT ADMINISTRATION

SPONSORED PROJECT TERMINATION SHEET

Date December 1, 1982

Project Title: Synthetic Studies on Sesquiterpenoids

Project No: G-33-642

Project Director: Dr. Drury S. Caine III

Sponsor: National Science Foundation

Effective Termination Date: 5/31/82

Clearance of Accounting Charges: 8/31/82

Grant/Contract Closeout Actions Remaining:

- [x] ~~Final Invoice and~~ Closing Documents
- [x] Final Fiscal Report
- [x] Final Report of Inventions
- [x] Govt. Property Inventory & Related Certificate
- [ ] Classified Material Certificate
- [ ] Other _____

Assigned to: Chemistry (School/~~Laboratory~~)

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Synthetic Studies on Sesquiterpenoids (NSF 7810044)

Technical Progress Report Period

Covered: August 24, 1979 - July 22, 1980

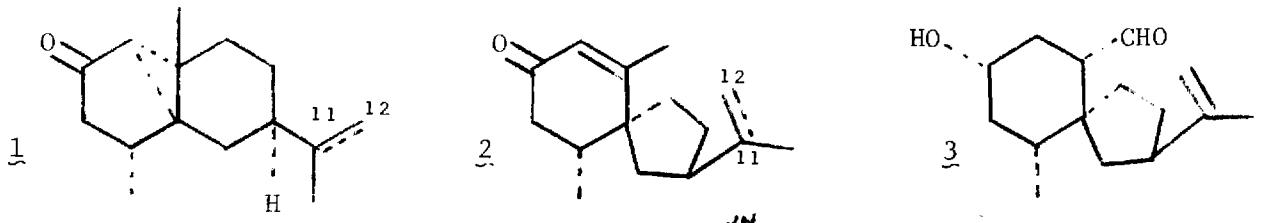
Synthetic Approaches to Phytuberin

A convenient, stereospecific synthesis of (+)-phytuberin from (-)-2-carone has been completed recently. The synthesis involved seven steps and the overall yield of the natural product was ~11%. The work has been submitted for publication in the J. Am. Chem. Soc. A preprint is attached. In connection with the work it was found the β-methyl-α,β-butenolides may be prepared by conjugate addition of lithium dimethylcuprate to γ-hydroxy acetylenic esters followed by addition of acid; β-methyl-α-allyl-α,β-butenolides could be obtained if the intermediate cuprate adduct was treated with allyl halides. This work has been accepted for publication in Synth. Commun. A preprint is attached.

Synthetic Approaches to Solavetivone and Lubimin

A publication covering our research on the synthesis and boron trifluoride-catalyzed rearrangement of the tricyclodecanone derivative 1a to produce 11,12-dihydrosolavetivone (2a) has been accepted for publication in the J. Org. Chem. A preprint is attached. Solavetivone (2b) has been obtained in low yield by a similar rearrangement of the tricyclodecanone 1b with an unsaturated side chain. Efforts to find an appropriate catalyst and reaction conditions which will provide an improvement in the yield of 2b are in progress.

We have been unable to devote much time to our proposed spiroannelation approach to solavetivone and lubimin (3). However, now that the synthesis



a. 11,12-bond sat'd; b. 11,12-bond sat'd.

of phytuberin has been completed we hope to begin intense investigation along this line within the next year.

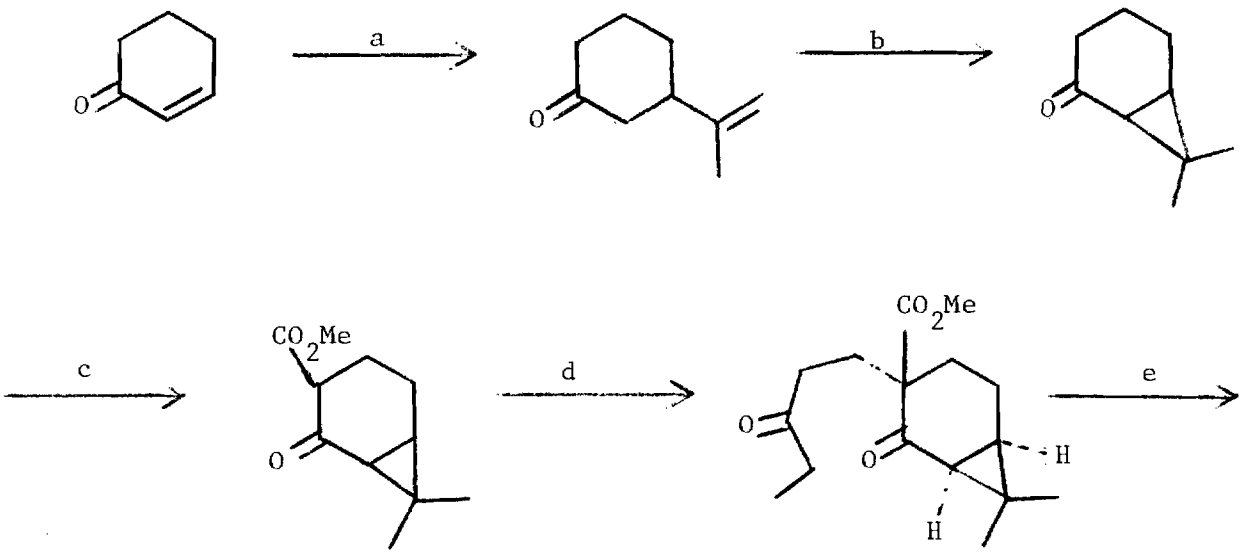
Approach to the Synthesis of Rishitin

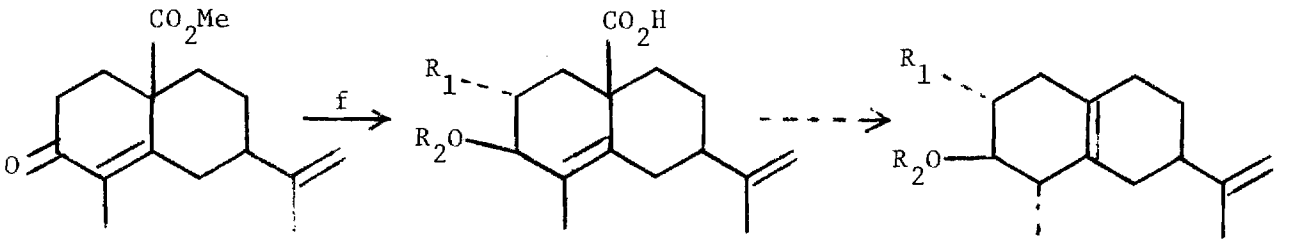
Scheme 1 shows the approach which we have followed in order to synthesize racemic rishitin (4a). A small quantity of the acetoxy acid 5b has been prepared. It is anticipated that thermal decarboxylation of this β,γ-unsaturated acid will lead to the unsaturated acetate 4b which will be hydrolyzed to 2-deoxyrishitin 4c. If the preparation of 4c is successful the 2α-hydroxy bicyclic acid 5a will be prepared from the keto ester 6 and converted into rishitin (4a) itself in a similar manner. Attempted decarboxylation of the hydroxy acid 5c gave the triene 7 presumably by formation of the lactone 8 followed by loss of carbon dioxide.

Synthetic Approaches to α,β-Butenolides and Related Compounds Using 2-β-Lithioacrylates

A series of β-bromo-α,β-butenolides 9 have been prepared by addition of bromo lithioacrylates such as 10 to aliphatic aldehydes and ketones. The β-bromo-α,β-butenolides 9 proved to be useful reagents for the synthesis of 2,2-disubstituted 3(2H)-furanones such as 11. The conversion involved the 1,2-addition of organometallic reagents (R_4M) to the carbonyl group in 9 followed by acid treatment. A paper covering the more important aspects of this research has been submitted to Tetrahedron Letters. A preprint is attached.

Scheme 1



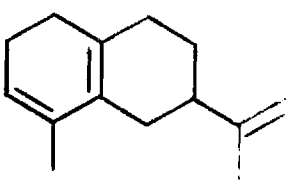


6 5 4

a. R_1=OH; R_2=Ac
b. R_1=H; R_2=Ac
c. R_1=R_2=H

a. R_1=OH; R_2=H
b. R_1=H; R_2=Ac
c. R_1=R_2=H

a. $CH_3C(MgBr)=CH_2$, Cu(I)Br; b. 1. HBr, 2. NaH; c. $(MeO)_2CO$, KH; d. KOH, Et_2O, $CH_3CH_2COCH=CH_2$; e. 1. HCl, 2. NaOAc; f. 1. $LiAlH(Ot\text{-}Bu)_3$, 2. KOH, H_2O, 3. AcCl, py.



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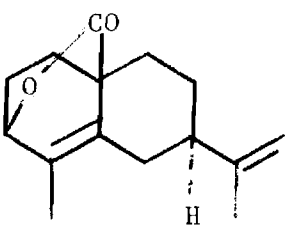

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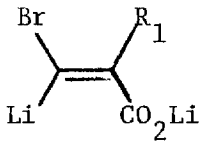

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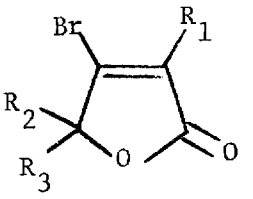

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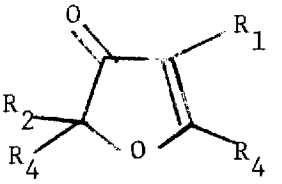
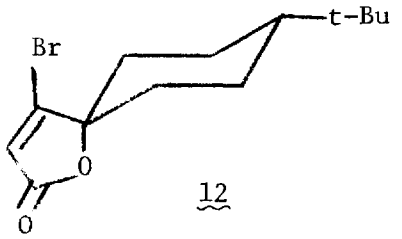


11

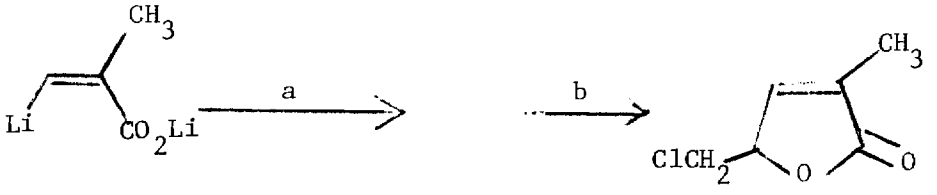
Other β-hetero-substituted lithioacrylates were found not to be as useful as 10 for butenolide synthesis. Reagent 10 (R_1 = H) reacted with 4-t-butylcyclohexanone to give the spiro butenolide 12 resulting from equatorial attach on the carbonyl group with high stereoselectivity.



12

We are attempting to improve the yields of lepiochlorin (13) and umbelactone (14) which have been prepared from the corresponding 2-β-lithioacrylates as shown in Schemes 2 and 3, respectively.

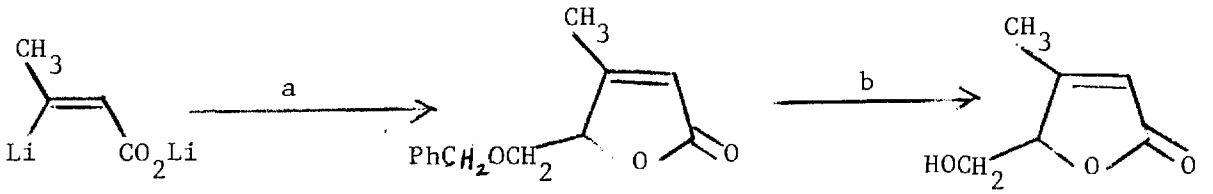
Scheme 2



13

a. $ClCH_2COCl$, ether, - 78°; b. H_3O^+

Scheme 3

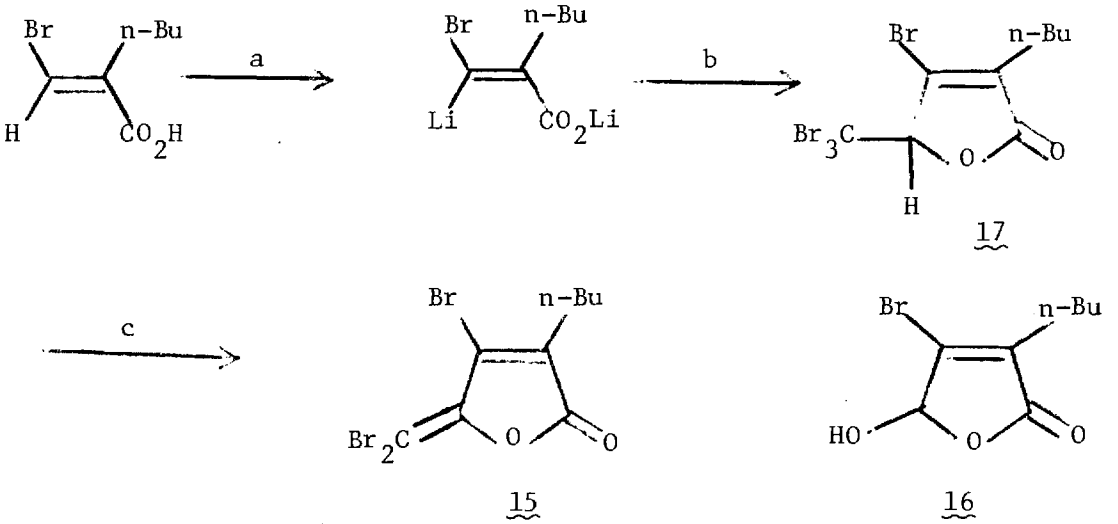


14

a. 1. $PhCH_2OCH_2CHO$, ether, -78°; 2. H_2O^+; b, H_3/Pd(C), EtOH

A route to the fimbrolide 15 (R. Kazlauskas, P. T. Murphy, R. J. Quinn, and R. J. Wells, Tetrahedron Lett., 1977, 37.) which is outlined in Scheme 4 is being explored. It is recognized that tribromoacetaldehyde may actually serve as a formylating agent for the lithium reagent so that the γ-hydroxybutenolide 16 and bromoform may be obtained rather than the desired butenolide 17. However, the simplicity of the route makes this investigation attractive.

Scheme 4



17

15 16

a. 2 equiv. n-BuLi, Et_2O, -78°; b. 1. Br_3CCHO, 2. H_3O^+; c. Mild base.

Residual Funds:

It is anticipated that no funds will be remaining at the end of the present support period, i.e. November 30, 1980.

Other Research Support:

Grants Pending:

A proposal on "The Synthesis of Antileukemic Terpenoids," which was submitted to the National Institutes of Health in October 1979 was approved for funding at a level of $34,221 (Direct Costs for the first year, (total of three years $96,704 (Direct costs)). However, it has not been established if funds will be available to support this project. A revision of this proposal was submitted to the National Institutes of Health in June, 1980. The budget request was for $34,896 (Direct Costs) for the first year; the total for three years was $104,048 (Direct Cost).

A Convenient, Stereospecific Synthesis of (+)-Phytuberin from (-)-2-Carone[1]

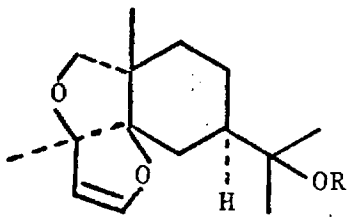
Sir:

Phytuberin (1a) is a sesquiterpene stress metabolite which has been isolated from fungal-infected potato tubers by Coxon and coworkers.[2] Its structure was established by spectroscopic methods and by an x-ray crystallographic structure determination on its 2,3-dihydro derivative. A lengthy biogenetic-like synthesis of 1a from α-cyperone, which established the absolute stereochemistry of the compound, was reported recently by Masamune and coworkers.[3] We wish to report a convenient, seven-step synthesis of 1a from (-)-2-carone (2) which allowed preparation of the natural product in 11% overall yield.

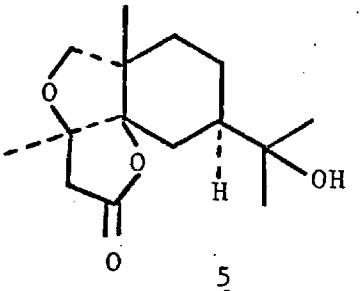
The four-stage retrosynthetic plan which we originally intended to follow for the 2 ⟶ 1a conversion is shown in Scheme 1. The first stage involved alkylation of the 2,3-enolate of 2 from the α side of the molecule to introduce a "protected" hydroxymethyl group at C-3. This would be followed by an acid-catalyzed solvolytic (using water or an alcohol) cleavage of the cyclopropane ring to produce a cyclohexanone derivative 3 having a trans relationship between the protected hydroxymethyl group and the oxyisopropyl side chain at C-5. In the second stage ketone 3 would be converted into a β-methyl spirobutenolide 4 with the new C-C bond cis to the protected hydroxymethyl group. It was planned that in stage three the tetrahydrofuran ring would be formed by an intramolecular Michael addition of the hydroxymethyl group (after deprotection) to the α,β-unsaturated lactone. This would yield deacetylphytuberin lactone 5, which has been prepared from phytuberin by Coxon's group.[2] Finally, it was felt that the lactone could be reduced to a lactol which could be

dehydrated to construct the dihydrofuran ring and produce deacetylphytuberin (1b), a derivative which could readily be converted into 1a. While this work was in progress, Masamune and coworkers[3] reported that a formyl spirobutenolide (derivable by oxidation of the primary hydroxy group in 4b) was converted directly into deacetylphytuberin by DIBAL-H reduction. It was expected that 4b would also undergo this biogenetic-like ring closure[4] on treatment with DIBAL-H. The employment of this transformation, which would avoid the intermediacy of 5, would reduce the number of steps in the sequence significantly.

Scheme 1



1 a. R=Ac
b. R=H



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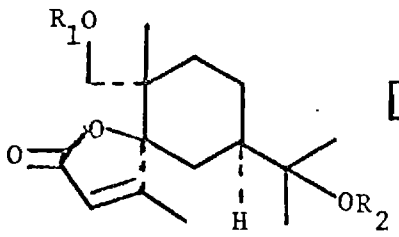
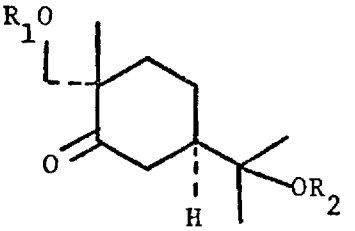
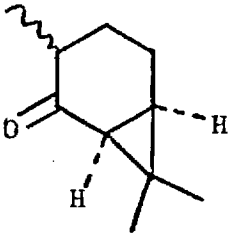


4 a. $R_1=R_2=CH_2Ph$
b. $R_1=R_2=H$

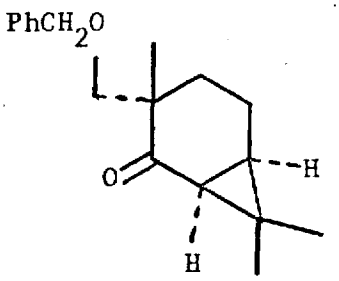


3 a. $R_1=CH_2Ph$; $R_2=H$
b. $R_1=R_2=CH_2Ph$



2

The cyclohexanone derivative 3 was obtained in a highly stereospecific manner. Alkylation of the lithium 2,3-enolate of 2 prepared under thermodynamic conditions using lithium diisopropylamide (LDA) as the base in tetrahydrofuran (THF))[5] with chloromethyl benzyl ether gave the bicyclic ketone 6[6] [65% yield; bp 120-126°C/0.05 mm; IR (CCl_4) 1692 cm^{-1} (C=O); NMR (CCl_4) δ 0.91 (s, 3 H), 1.02 (s, 3 H), 1.10 (s, 3 H), 3.17 and 3.49 (ABq, J = 8.6 Hz, 2 H, $O-\underline{CH_2}-\overset{|}{C}-$) 4.42 (s, 2 H, $C_6H_5\underline{CH_2}O-$), 7.23 (s, 5H, $-C_6H_5$)] as a single product. The cyclopropane ring in 6 was readily cleaved with aqueous acid to give 3a. However to avoid having to protect the tertiary hydroxy group in a separate step, ketone 6 was treated with benzyl alcohol containing a catalytic amount of p-toluenesulfonic acid to give directly the dibenzyl derivative 3b[6] [85% yield; IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 1.07 (s, 3 H), 1.25 (s, 6 H), 3.17 and 3.39 (ABq, J = 9.2 Hz, 2 H, $-OCH_2-\overset{|}{C}-$), 4.35 (s, 2 H, $C_6H_5\underline{CH_2}O-$), 4.44 (s, 2 H, $C_6H_5\underline{CH_2}O-$), 7.21 (s, 10 H, 2 C_6H_5's)].



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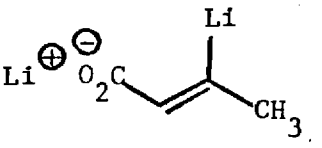

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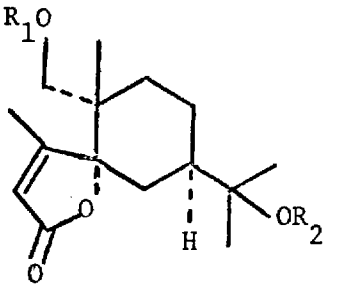
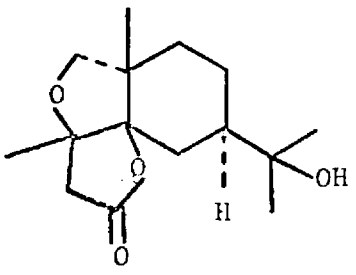


8 a. $R_1=R_2=CH_2Ph$

b. $R_1=R_2=H$



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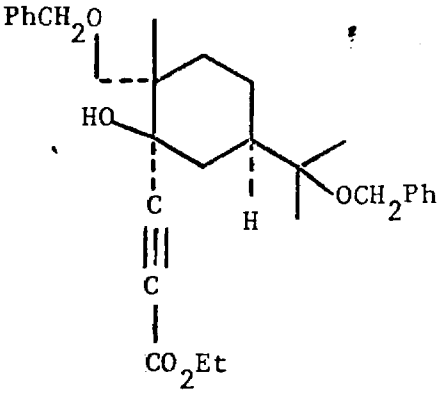

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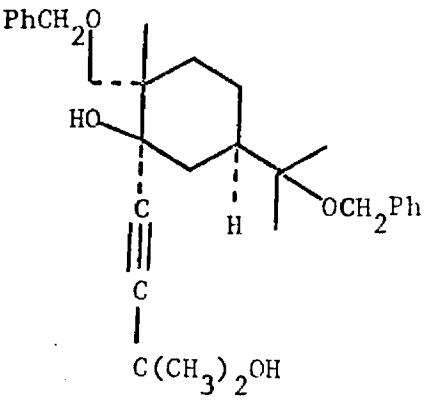

11

We hoped to utilize methodology analogous to that which was reported recently for a direct conversion of ketone 3b into the β-methyl spirobutenolide 4a.[7] Thus, 3b was reacted with the β-lithioacrylate derivative 7 (prepared by treatment of Z-3-bromobutenoic acid with 2 equiv of n-butyllithium in ether at -78°C) under the conditions described previously for the conversion of ketones into butenolides.[7] This led to the formation of a ca. 12:88 mixture of the isomeric spirobutenolides 4a and 8a in 45-51% yield. The isomers which were separated by chromatography on silica gel exhibited the following spectral properties: 4a[6] [IR (CCl_4) 1755 (α,β-unsaturated γ-lactone C=O), 1637 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 1.09 (s, 3 H), 1.19 (s, 6 H), 2.08 (d, J = 1.6 Hz, 3 H), 3.18 and 3.41 (ABq, J = 9.0 Hz, 2 H), 4.45 (s, 2H), 4.61 (s, 5 H), 7.22 (s, 5 H), 7.27 (s, 5 H); 8a[6] [IR (CCl_4) 1764 (C=O), 1637 cm^{-1} (C=C); NMR (CCl_4) δ 1.22 (s, 6 H), 1.27 (s, 3 H), 1.98 (d, J = 1.8 Hz, 3 H), 2.96 and 3.27 (ABq, J = 9.0 Hz, 2 H), 4.25 (s, 2 H), 4.35 (s, 2 H), 5.43 (q, J = 1.8 Hz, 1 H), 7.17 (s, 10 H)].

Hydrogenation of the minor isomer 4a in 95% ethanol containing 10% Pd(C) allowed quantitative removal of the benzyl protecting groups without reduction of the conjugated double bond to give the diol 4b. When 4b was allowed to stand on basic alumina[8] for 1 h and then eluted with 50% ether-hexane, deacetylphytuberin lactone 5, which showed identical spectral properties to those of an authentic sample[2,9] was isolated in 88% yield. Application of a similar sequence to the major butenolide led via 8b to the tricyclic hydroxylactone 9[6] [mp 61-62°C; IR (CCl_4) 3620, 3480 (OH), 1772 (C=O), 1382, 1368, 1117, 1040, 1017, 906 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (s, 9 H), 1.40 (s, 3 H), 2.52 and 2.82 (ABq, J = 18 Hz, 2 H), 3.63 (s, 2 H)]. Since the addition of the vinyllithium reagent 7 to the carbonyl group in 3b occurred predominately from the undesired equatorial direction, it was clear that a method which would lead to the

butenolide 4a stereoselectively would have to be sought.

It was felt that the addition of a relatively small carbanionic species such as acetylide ion to the carbonyl group in 3b might occur predominately from the axial direction.[10] In a model study it was found that addition of lithium carboxyethylactylide[11] to 4-t-butylcyclohexanone occurred almost exclusively in the axial manner; and, furthermore, it was observed that the resulting γ-hydroxy acetylenic ester was converted into the corresponding anti β-methyl spirobutenolide by reaction with 2 equiv of lithium dimethylcuprate.[12] Thus it appeared that an analogous two-step process might be applicable to the 3b ⟶ 4a conversion. Indeed, the first step proceeded readily and the γ-hydroxyacetylenic ester 10[6] [92% yield; IR (CCl_4) 3495 (OH), 2225 (C≡C), 1715 cm^{-1} (C=O); NMR (CCl_4) δ 1.08 (s, 3 H), 1.21 (s, 6 H), 1.30 (t, J = 7.4 Hz, 3 H), 3.19 and 3.79 (ABq, J = 8.9 Hz, 2 H), 4.18 (q, J = 7.4 Hz, 2 H), 4.40 (s, 2 H), 4.56 (s, 2 H), 7.22 (s, 5 H), 7.28 (s, 5 H)] formed by axial addition was obtained when 3b was reacted with lithium carboxyethylacetylide in THF at -78° for 1.0 h. The stereochemistry of 10 was confirmed by the subsequent transformations. None of the isomeric γ-hydroxyester which could have resulted from equatorial addition to 3b was isolated.

Considerable difficulty was encountered in finding proper conditions to effect the 10 ⟶ 4a conversion. When 10 was treated with 2 equiv of lithium dimethylcuprate in THF at ca. -10° for 3 h under the same conditions which were used to convert the adduct of lithium carboxyethylacetylide and 4-t-butylcyclohexanone into the corresponding anti β-methyl spirobutenolide,[12] only unchanged starting material was recovered. When the cuprate addition was run in THF at 0-25°C using 2-10 equiv of reagent, the tertiary alcohol 11[6] [mp 97.5-98.5°C, IR(CCl_4) 3620, 3520 (OH), 2230 cm^{-1}

(C≡C); NMR (CCl_4) δ 1.10 (s, 3 H), 1.20 (s, 6 H), 1.43 (s, 6 H), 3.16 and 3.78 (ABq, J = 8.6 Hz, 2 H), 4.40 (s, 2 H), 4.53 (s, 2 H), 7.23 (s, 5 H), 7.35 (s, 5 H),] which resulted from 1,2- addition of the cuprate to the carboxyethyl group, was the only product isolated. When the reaction was carried out at temperatures below -10° for extended reaction times using 2 equiv of lithium dimethylcuprate in ether, mixtures of the butenolides 4a, the acetylenic diol 11, and the starting material were isolated. However, best results were obtained when 10 was reacted with 1 equiv of lithium dimethylcuprate in ether at -24°C for 84 h. This led to the formation of a ca. 3:1:1 mixture of 4a, 11, and 10. Chromatography of the mixture on silica gel allowed the isolation of 4a in 60% yield, based on consumed starting material.

In order to form the tetrahydro and dihydrofuran rings in phytubein, diol 4b, which was prepared by hydrogenolysis of the benzyl groups in 4a, was reacted with 3.5 equiv of DIBAL-H (-40°C, 1.0 h; 0°C, 0.5 H).[3] Work up of the mixture with 2 N NaOH gave deacetylphytuberin (1b) in 63% yield. This material exhibited identical spectral properties to those of an authentic sample.[2,9] Acetylation of 1b (Ac_2O, Et_3N, cat. amt. of 4-N,N-dimethylaminopyridine[14]) gave 71% of (+)-phytuberin (1a) having identical IR and NMR spectral properties and TLC behavior to an authentic sample.[9]

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1. This research was supported by a grant (NSF #7810044) from the National Science Foundation for which we are grateful.

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gave C-1 rather than C-3 alkylation products.

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THE SYNTHESIS OF SUBSTITUTED α,β-BUTENOLIDES FROM γ-HYDROXY-α,β-ACETYLENIC ESTERS

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The α,β-butenolide ring system is found in a number of physiologically important natural products[2] and there has been recent interest in the development of methods of synthesis of compounds of this type.[3] It is well known that α,β-unsubstituted butenolides may be prepared by catalytic hydrogenation of γ-hydroxy acetylenic acids.[4,5b] Recently, an excellent route of γ-hydroxy acetylenic esters which involves the addition of the lithium acetylide salts of propiolic esters to aldehydes[5] and ketones[6] has become available. We have carried out the addition of ethyl lithiopropiolate (1) to cyclohexanone (2) and 4-t-butylcyclohexanone (3) and wish to report the conversion of these adducts into corresponding β-methyl or β-methyl-α-allyl-α,β-butenolides.

1-[2-(Carboethoxy)ethynyl]cyclohexanone (4), the adduct of 1 and 2, was prepared according to the procedure described by Schlessinger and coworkers.[5b,c] This procedure was similar to that described for Midland and coworkers,[6] except that lithium diisopropylamide (LDA) was

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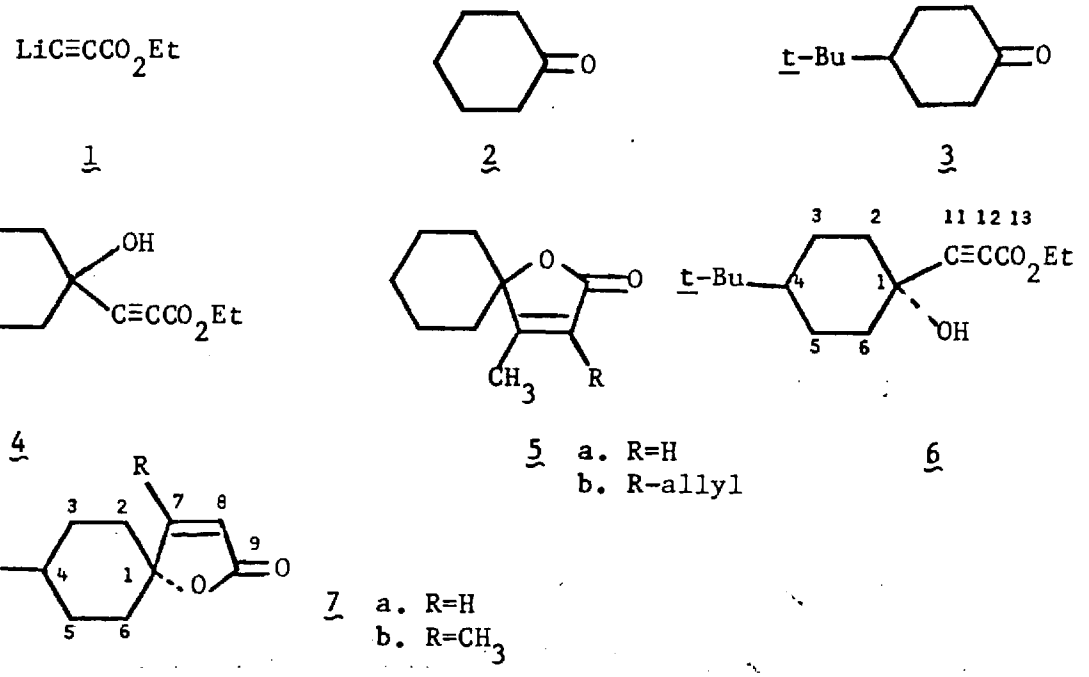
used as the base for the preparation of 1. The conjugate addition of lithium dialkylcuprates to α,β-acetylenic esters provides a method of sterospecific synthesis of tri- and/or tetra-substituted olefins.[7] Treatment of adduct 4 with 2 equiv. of lithium dimethylcuprate, prepared from reaction of methyllithium with the cuprous bromide-dimethylsulfide complex,[8] in anhydrous ether for 16 h at -78°C followed by acidification with hydrochloric acid gave the known β-methylbutenolide 5a[9] in 84% yield.[10]

Additions of lithium dialkylcuprates to acelytenic esters are presumed to proceed via α-carboalkoxy vinyl copper intermediates.[7] Such species have been reacted with allylic halides to yield α-substituted-α,β-unsaturated esters.[11] Thus, when dry hexamethylphosphoramide (HMPA) (~10% by volume) followed by 4.3 equiv. of allyl bromide was added to the reaction mixture obtained from addition of lithium dimethylcuprate to 4, the α-allyl-β-methyl-α,β-butenolide 5b was obtained in 71% yield after acidification with hydrochloric acid and distillation.

Additions of metal acetylides to 4-t-butylcyclohexanone occur mainly from the axial direction with respect to the carbonyl group.[12] Upon reaction of 1 with 3 the acetylenic carbinol 6 was obtained in 84% yield. The stereochemistry of the adduct 6 was established by converting it into the butenolide 7a by catalytic hydrogenation in 95% ethanol containing quinoline using 5% palladium on barium sulfate as the catalyst. Butenolide 7a was found to be identical to the minor product of addition of lithium Z-β-lithioacrylate to 3.[3e] Treatment of 6 with lithium dimethylcuprate



according to the procedure described by Carlson and coworkers[7c] gave α-methyl-α,β-butenolide 7b in 76% yield.[10] Methodology analogous to that described above should be generally useful for the synthesis of other β-alkyl or β-alkyl-α-allyl-α,β-butenolides.

EXPERIMENTAL SECTION[13]

1-[2-(Carboethoxy)-ethynyl]cyclohexanol(4)[5b,c] - Dry diisopropylamine (2.86 ml, 20.4 mmol) was added to 25 ml of dry tetrahydrofuran (THF) and the solution was cooled to -10°C and treated with 8.68 ml of 2.35 M n-BuLi in hexane. The mixture was stirred for 15 min and then cooled to -78°C. Ethyl propiolate (2.00 g, 20.4 mmol) was then added slowly, the reaction mixture was stirred for 1 h, and then 2.00 g (20.4 mmol) of cyclohexanone in 5 ml of dry THF was added dropwise. The mixture was stirred overnight (~16 h) at -78°C and 40 ml of 1:1 conc hydrochloric

acid-water was added. The mixture was then diluted with 100 ml water and extracted with four 50 ml portions of ether. The combined ethereal extracts were washed with 50 ml of saturated $NaHCO_3$ and 50 ml of saturated NaCl. The solution was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. Distillation of the residue gave 3.21 g (83%) of the ethynyl carbinol 4;[6] bp 112-113° (bath temperature)/ 0.18 mm; IR (CCl_4) 3610, 3470, 2230, 1718 cm^{-1}; ^1H NMR (CCl_4) δ 1.33 (t, 3H, J = 7.2 Hz), 4.27 (q, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 68.9 (s), 38.8 (t), 22.7 (t), 24.9 (t), 38.8 (t), 75.6 (s), 90.3 (s), 153.1 (s), 61.8 (t), 14.0 (q); MS (70 eV) m/e 196(1), 125(100).

1-Oxa-4-methylspiro[4.5]dec-3-en-2-one(5a)[10] - Methyllithium (3.06 ml, 1.4 M in ether) was added dropwide to a stirred slurry of $CuBr \cdot S(CH_3)_2$ in 15 ml of anhydrous ether at 0°C. The mixture was allowed to stir for 15 min, cooled to -78°C, and 0.200 g (1.2 mmol) of the ethylnyl carbinol 4 in 2 ml of anhydrous ether was added. The mixture was stirred for 14.0 h at -78°C and allowed to warm to room temperature and stirred for an additional 4.0 h. It was then poured into ~50 ml of cold 1 N hydrochloric acid and stirred for 1.0 h. The aqueous phase was extracted with four 25 ml poritions of ether and the combined etheral extracts were washed with 50 ml of saturated $NaHCO_3$ followed by 50 ml of saturated NaCl and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was distilled to yield 0.144 g (85%) of the butenolide 5a:[9,3e] bp 110-115°C (bath temperature)/0.2 mm; mp 49-51°C; IR (CCl_4) 1761 and 1648 cm^{-1}; ^1H NMR (CCl_4) δ 2.00 (d, 3H, J = 1.8 Hz) and 5.59 (q, 1H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$)[14] δ

88.5 (s), 33.1 (t), 21.8 (t), 24.5 (t), 21.8 (t), 33.1 (t), 171.5 (s) 114.9 (d), 172.8 (s), and 13.2 (q).

1-Oxa-4-methyl-3(1-prop-2-enyl)spiro[4.5]dec-3-en-2-one(5b) - Methyllithium (6.48 ml, 1.40 M in ether) was added dropwise to a stirred slurry of 1.07 g (5.19 mmol) of $CuBr \cdot S(CH_3)_2$ in 25 ml of anhydrous ether at -6°C. The mixture was allowed to stir for 30 min, cooled to -78°C, and 0.424 g (2.16 mmol) of 4 in 3 ml of anhydrous ether was added. The mixture was stirred for 12.0 h at -78° and allowed to warm to room temperature and stirred for an additional 4 h. The mixture was cooled to 0°C and 2.5 ml of anhydrous HMPA and 1.1 g (9.3 mmol) of allylbromide in 3 ml of anhydrous ether was added. The mixture was stirred for 1.0 h at 0°C and worked up as described above to yield 0.315 g (71%) of the butenolide 5b; bp 118-122°C (bath temperature)/0.1 mm; IR (CCl_4), 3075, 1760, 1675, and 1635 cm^{-1}; ^1H NMR (CCl_4) δ 1.95 (s, 3H), 2.93 (broad d, 2H, J = 6.0 Hz); 5.00 (dm, 2H), and 5.83 (ddt, 1H, J = 9.5, 18.0, and 6.0 Hz); ^{13}C NMR ($CDCl_3$)[14] δ 86.9 (s), 33.3 (t), 21.8 (t), 24.5 (t), 21.8 (t), 33.3 (t), 165.0 (s), 123.0 (s), 172.2 (s), 11.2 (q), 27.3 (t), 132.9 (d), 115.2 (t); MS (70 eV) m/e 206.1303 (calc 206.1307); 79 (100). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.70; H, 8.82.

trans-4-t-Butyl-1-[2-(carboethoxy)-ethynyl]cyclohexanol (6)[5b] - Dry diisopropylamine (1.96 g, 19.4 mmol) was added to 20 ml of anhydrous THF and the solution was cooled to -10°C and treated with a 8.78 ml of 2.21 M n-BuLi in hexane. The mixture was stirred for 15 min and cooled to -78°C. Ethyl propiolate (1.91 g, 19.4 mmol)

was then added slowly, the mixture was stirred for 1 hr, and 3.00 g (19.4 mmol) of 4-t-butylcyclohexanone in 5 ml of anhydrous THF was added. The mixture was stirred 16 h at -78°C and treated with 50 ml of 1:1 conc. hydrochloric acid-water. Work up of the mixture as described for 4 gave 4.10 g (94%) of the ethynyl carbinol 6; mp 54-55°C; IR (CCl_4) 3610, 3420, 2230 and 1721 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (s, 9H), 1.30 (t, 3H, J = 7.4 Hz), 4.16 (q, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$)[14] δ 68.9 (s), 39.5 (t), 24.6 (t), 46.8 (d), 24.6 (t), 39.5 (t), 32.1 (s), 27.4 (q), 27.4 (q), 27.4 (q), 76.4 (s), 89.9 (s), 153.0 (s), 61.6 (t), 14.0 (q); MS (70 eV) m/e 252.1735 (Calc for $C_{15}H_{24}O_3$ 252.1725).

1-Oxa-7-t-butylspiro[4.5]dec-3-en-2-one 7a:[5b] - A mixture of 1.15 g (4.56 mmol) of the ethynyl carbinol 6 in 5 ml of 95% ethanol containing 56 μL of quinoline and 58 mg of 5% $Pd/BaSO_4$ was stirred under a hydrogen atmosphere at 25° until the theoretical quantity of hydrogen had been taken up. The mixture was then filtered to remove the catalyst and the solvent was removed under reduced pressure. The residue was poured into 50 ml of cold 10% hydrochloric acid and stirred for 2 h. Ether (100 ml) was added and after shaking the mixture the layers were separated. The aqueous layer was then extracted with two 50 ml portions of ether and the combined ethereal extracts were washed with 50 ml saturated $NaHCO_3$, 50 ml of saturated NaCl, and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave 0.868 g (91%) of the butenolide: IR (CCl_4) 1771 and 1608 cm^{-1}; NMR (CCl_4) δ 0.93 (s, 9H), 5.97 (d,

1H, J = 5.8 Hz), 7.80 (d, 1H, J = 5.8 Hz); MS (70 eV) 208 (56), 151 (100). Butenolide 7a exhibited identical GLC behavior to the minor butenolide component prepared by addition of lithium Z-β-lithioacylate to 4-t-butylcyclohexanone.[3e]

1-Oxa-4-methyl-7-t-butylspiro[4.5]dec-3-en-2-one (7b)[7c] - A slurry of freshly purified CuI in 40 ml of anhydrous THF was stirred and cooled to -10°C and 12.7 ml of methyllithium (1.31 M in ether) was added slowly. The mixture was stirred for 30 min at -10° and a solution of 1.00 g (3.96 mmol) of ethynyl carbinol 6 in 5 ml of anhydrous THF was added. The mixture was stirred at -10°C for 3 h and poured into 100 ml of 10% hydrochloric acid and stirred vigorously for 1.0 h. It was then extracted with four 50 ml portions of ether and the combined ethereal extracts were washed with two 50 ml portions of saturated $NaHCO_3$, one 50 ml portion of saturated NaCl, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give 0.70 g (76%) of the butenolide 7b; mp 87-88°C; IR (CCl_4) 1762 and 1635 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (s, 9H), 2.20 (d, 3H, J = 1.4 Hz), and 5.57 (q, 1H, J = 1.4 Hz); ^{13}C NMR ($CDCl_3$)[14] δ 88.3 (s), 34.0 (t), 23.5 (t), 44.9 (d), 23.5 (t), 34.0 (t), 171.2 (s), 115.8 (d), 172.5 (s), 16.6 (q), 32.3 (s), 27.4 (q), 27.4 (q), and 27.4 (q); MS (70 eV) m/e 222.1628 (calc 222.1620); 57 (100).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.83; H, 10.00.

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Acid-Catalyzed Rearrangements of Cyclopropyl Ketones Related to Eudesmane[1]

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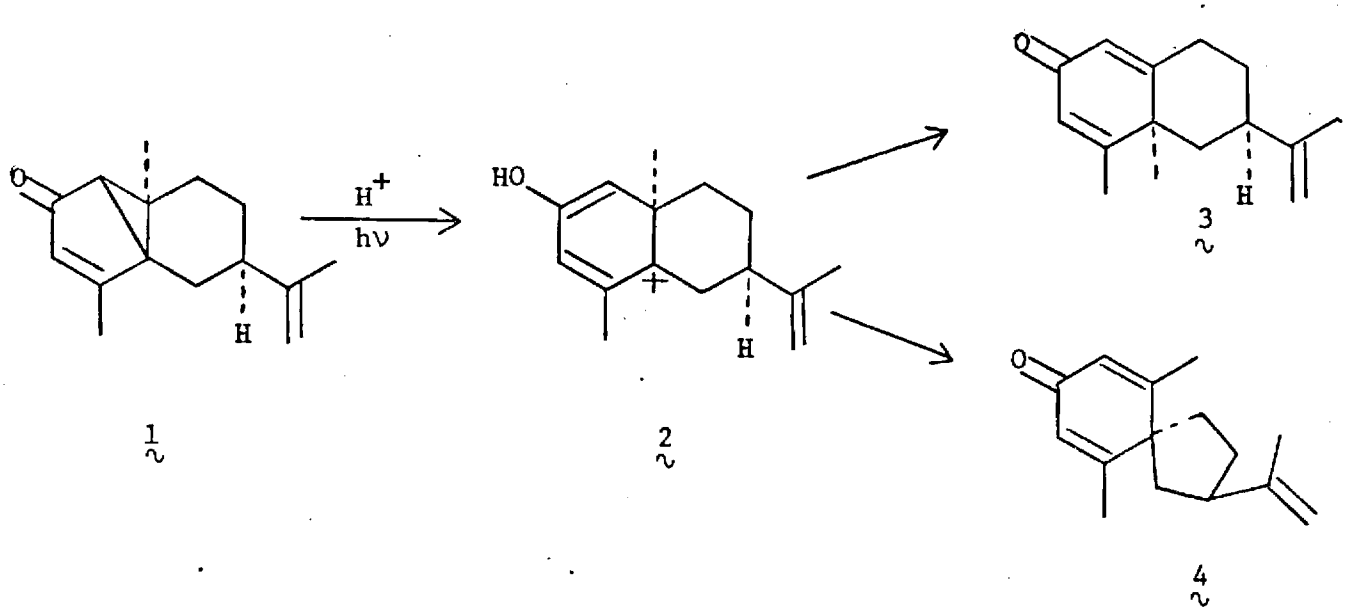
Abstract

Tricyclodecenones 5, 6, 7 have been synthesized. Upon reaction with the Lewis acid, boron trifluoride, in methylene chloride these compounds underwent opening of the cyclopropane ring and rearrangement of the carbon skeleton. Cyclopropyl ketones 5 and 7 which are stereochemically related to 10-epieudesmane gave 11,12-dihydronootkatone (11) and the octalone derivative 12a, respectively, as the major products, upon treatment with boron trifluoride. In each case these products apparently arose via opening of the internal (2,6) bond of the cyclopropane ring followed by a 1,2-shift of the 1-methyl group to C-6. On the other hand, cyclopropyl ketone 6 which is stereochemically related to eudesmane gave 11,12-dihydrosolavetivone (13) as the major product upon treatment with boron trifluoride. This spirocyclic enone apparently was produced by opening of the internal bond of the cyclopropane and a 1,2-shift of the 1-methylene group to C-6.

The currently accepted biogentic pathways for the formation of nootkatone (eremophilane) or spirovetivane sesquiterpenes involve 1,2-methyl or methylene migrations in bicyclic carbonium ions related to eudesmane.[2] In recent years there has been a considerable amount of interest in the duplication of rearrangements of these types in the laboratory.[3,4] In the accompanying paper we reported that nootkatane and spirovetivane sesquiterpenes may be interconverted by photochemical pathways.[4] In this work bicyclic or spirocyclic intermediates containing a cross-conjugated cyclohexadienone chromophore in ring A were converted into the corresponding tricyclodecenone derivatives (lumiproducts) by irradiation in dioxane at 254 nm. These lumiproducts were then irradiated in aqueous acetic acid with greater than 300 nm wavelength ultraviolet light to produce dienone products with the appropiate sesquiterpene skeletons.

The types of photochemical rearrangements described above can be illustrated using the tricyclodecenone derivative 1, which is related to 10-epieudesmane. Light-induced cleavage of the internal bond of the cyclopropane ring in 1 apparently leads to the bicyclic carbonium ion 2 which may undergo 1,2-methyl migration to produce dehydronootkatone (3) or 1,2-methylene migration to produce anhydro-β-rotunol(4). The latter pathway is significantly favored since the initial ratio of 3 to 4 was 1:5.6.[4]

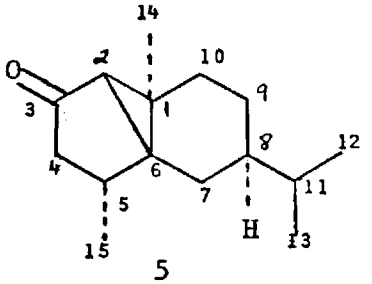


1 2 3 4

Conjugated cyclopropyl ketones are known to react readily with a variety of electrophilic reagents. Upon treatment with (1) halogen acids in ethanol or acetic acid they undergo ring opening to yield γ-halo ketones,[5] (2) with protic or Lewis acid catalysts in nucleophilic solvents they yield ketones derived from ring opening followed by proton transfer or incorporation of the solvent at the γ position,[5b,6] and (3) in systems where structural features permit, the ring opening process may be accompanied by olefin or aryl participation[7] or rearrangement of the carbon skeleton[8] when Lewis acids in aprotic solvents are used as the electrophilic reagents.

The latter results indicated that reactions of tricyclodecanone derivatives related to 1 with Lewis acid catalysts in aprotic solvents might lead to rearrangement products having a nootkatone and/or a spirovetivane ring skeleton. Therefore, we have synthesized the diastereomeric tricyclodecanones 5[9] and 6, which have a carbon skeleton related to eudesmane, and the tricyclodecanone 7, having a 9α rather than an 8β-isopropyl group, and have investigated the reactions of these compounds with boron trifluoride in methylene chloride.

Cyclopropyl ketone 5 was readily obtained from dienone 1[4] by catalytic hydrogenation over palladium-on-carbon in ethanol. Cyclopropyl ketone 7 was prepared in a similar manner by catalytic hydrogenation of the corresponding dienone 8[4]. Examination of models of both 1 and 8 clearly indicated that the β side of the 4,5 double bond was much less hindered than the α side. The stereochemistry of 5-methyl groups in 5 and 7 was assigned on the basis of the assumption that hydrogen would be added from the less hindered side of the double bond. These assignments were confirmed by the subsequent rearrangement reactions described below.



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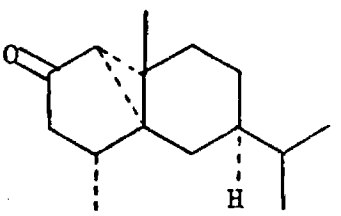

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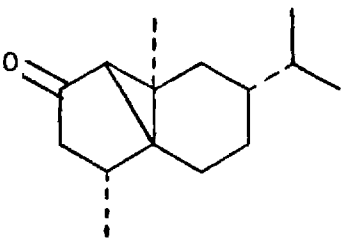

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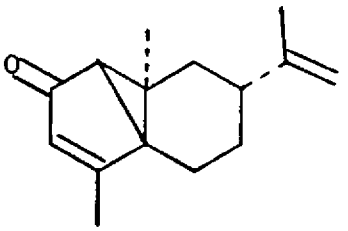

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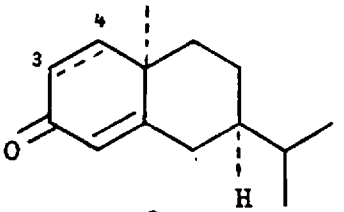
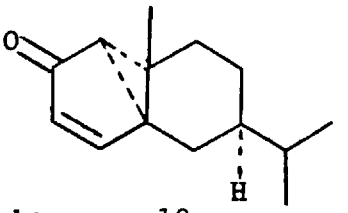


9 a. 3,4-bond sat'd
b. 3,4-bond unsat'd

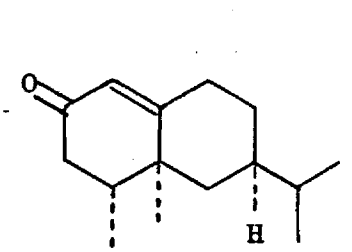


10

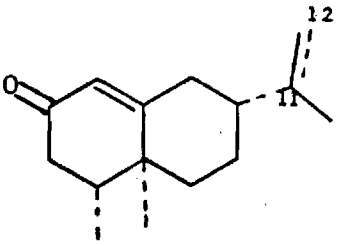
Cyclopropyl ketone 6 was prepared by conversion of the known enone 9a [10] into the corresponding cross-conjugated dienone 9b by the phenylseleneylation-selenoxide elimination procedure,[11] photochemical rearrangement of 9b to the tricyclodecenone 10 by irradiation with 254 nm ultraviolet light in anhydrous dioxane, and conjugate addition of lithium dimethylcuprate to the enone system using the procedure of House and coworkers.[12] In the latter reaction a single product was obtained in ca. 95% yield. The 1β-methyl in 10 would provide a considerable amount steric hindrance to the approach of the cuprate reagent from the β side of the 4,5 double bond. Thus it was assumed that the conjugate addition product contained a 5α-methyl group as indicated in 6. This stereochemical assignment was supported by subsequent experiments.

Ketone 5 was allowed to react with a saturated solution of boron trifluoride in dry methylene chloride for 24 h. at room temperature. GLC analysis of the reaction mixture indicated that essentially all of the starting material had been consumed and one major product which made up greater than 65% of the volatile compounds had been formed. The mixture also contained four minor components, but none of these amounted to as much as 10% of the total volatile material. The major product was isolated by chromatography on silica gel. Its spectral properties indicated that it was a bicyclic enone. These properties as well as the GLC behavior of the product

were found to be identical to those of an authentic sample of 11,12-dihydronootkatone (11), which was prepared by selective hydrogenation of natural nootkatone[13] using the homogeneous catalyst tris(triphenylphosphine)rhodium in benzene.[14]



11



12

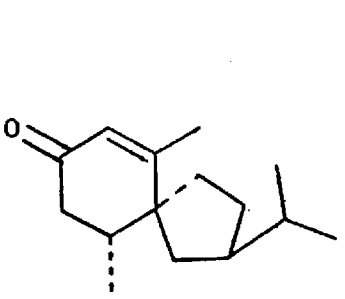
a. 11,12-bond saturated
b. 11,12-bond unsaturated

The minor components of the reaction of 5 could not be isolated in sufficiently pure form to permit positive identification. However, examination of the spectral properties of partially purified materials indicated that a mixture of unconjugated bicyclic enones resulting from cleavage of the 2,6-bond of the cyclopropane ring and proton transfer from C-5 and C-7 and a cyclopentenone derivative resulting from cleavage of the 1,6-bond and migration of the 7-methylene group to C-1 probably were produced. Products of similar structures were observed to be formed in small amounts when a steriodal cyclopropyl ketone related to 5 was reacted with Lewis acids.[8b] No evidence for the formation of any spirocyclic enone which would result from concomitant cleavage of the 2,6-bond and migration of the 10-methylene group to C-6 was obtained.

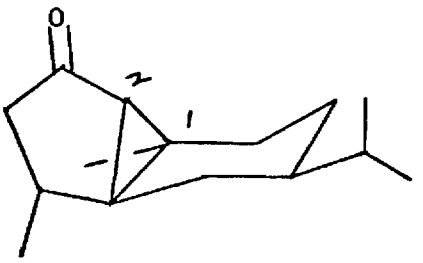
Cyclopropyl ketone 7 was treated under the same conditions as those described for the isomer 5. In this case GLC analysis indicated that only two products were formed in a ~9:1 ratio in ~80% yield. The major component was purified by preparative GLC. It exhibited identical GLC behavior and spectral properties to those of a sample of the enone 12a which was prepared from dienone 12b[4] by selective hydrogenation of the 11,12 double bond using tris(triphenylphosphine)rhodium chloride in benzene.[14] The minor component of the acid-catalyzed reaction of 7 was not identified.

However, GLC and spectral evidence indicated that a spirocyclic product, i.e., 11,12-dihydrosolavetivone (13), which could have been formed by opening the 2,6-bond and migration of the 10-methylene group to C-6, was not produced.

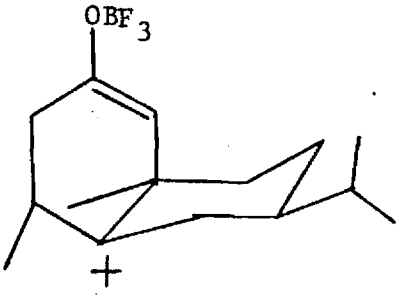
The reaction of cyclopropyl ketone 6 with boron trifluoride was investigated next. When treated as described above it yielded one major product and two minor components in an 18:1:1 ratio by GLC. The yield of volatile products was ~80%. The major product was purified by preparative TLC. It exhibited identical spectral properties and chromatographic behavior (GLC and TLC) to an authentic sample of 11,12-dihydrosolavetivone (13) which was obtained by selective hydrogenation of the double bond in the isopropenyl group of (-)-solavetivone[15] using tris(triphenylphosphine)rhodium chloride in benzene. Insufficient quantities of the minor components of the reaction of 6 were available to permit identification.



13



5A

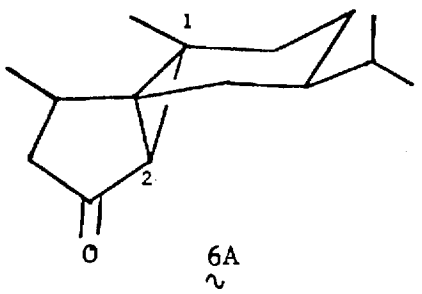


14

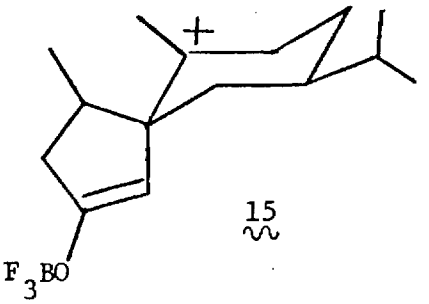
The formation of 11,12-dihydronootkatone (11) from cyclopropyl ketone 5 involves cleavage of the internal (2,6) bond of the three-membered ring and migration of the 1-methyl group to C-6. In the relatively non-polar solvent methylene chloride it is possible that the entire process is concerted, since bond cleavage and bond formation can occur from the opposite sides of C-6. However, it may be formally represented as proceeding via a bicyclic carbonium ion intermediate. The most favorable conformation of ketone 5 would be expected to be 5A in which the isopropyl group is equatorial to the six-membered ring. In 5 the external (1,2) bond of the cyclopropane ring overlaps more favorably than the internal bond with the pi orbital of the carbonyl group. However, in 5A cleavage of the 2,6 bond can occur in a diaxial manner leading to a bicyclic carbonium ion in conformation 14 in which the enolized carbonyl function is axial with respect to the B ring.[6b] In

this species, a transition state which allows for maximum orbital overlap during migration to C-6 appears to be much more easily acheived by the methyl group than the methylene group. The establishment of a conjugated enone system apparently provides a strong driving force of a rearrangement reaction as opposed to proton transfer processes which would lead to unconjugated bicyclic enones.[16] However, as noted above proton transfer products were possibly produced in small quantities from 5. The same conformational and electronic factors which are involved in the arrangement of 5 to 11 also seem to account for the formation of the octalone 12a from the tricyclodecenone 7.

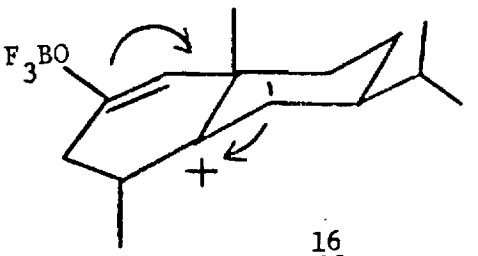
We were surprised to find that cyclopropyl ketone 6 gave primarily the spiro enone 11,12-dihydrosolavetivone (13), on reaction with boron trifluoride. The most favorable conformation of 6 should be as represented in 6A in which opening of the external (1,2) bond could occur in a diaxial sense. Thus products formally arising from rearrangement via the spiro carbonium ion intermediate 15 were expected in this case.



6A



15



16

Indeed, we have observed that reaction of the 5-nor methyl derivative of 6 with hydrogen bromide in acetic acid led mainly to a spirocyclic bromoketone resulting from opening of the three-membered ring in the diaxial manner.[5a] (In contrast, the nor methyl derivative of 5 gave exclusively a bicyclic bromoketone again by a pathway also involving cleavage of the ring in a diaxial manner).[5a] However, it seems that spiro enone 13 would have to arise from migration of the 10-methylene group to C-6 in a bicyclic

carbonium ion intermediate. It is possible that the spiro carbonium ion 15 is formed initially but arranges to a bicyclic species with a conformation such as 16, in which steric interaction between the methyl group at C-5 and the 7-methylene groups is minimized and the 10-methylene group is favorably disposed for migration, faster than other reactions occur.[17] In the conversion of 6 into 13 cleavage of the 2,6-cyclopropyl bond and formation of the new carbon-carbon bond by methylene migration must occur from the same side of C-6. Therefore, the possibility of a concerted methylene migration seems less likely here than in the systems in which methyl migration was observed.

The above mechanistic arguments are based upon the assumption that the reaction products were produced under kinetic control. The bicyclic and spiro cyclic enones which were formed were shown to be stable under the reaction conditions. We cannot rule out the possibility that other undetected conjugated enones or bicyclic or spirocyclic unconjugated enones derived from proton transfer reactions in carbonium ions such as 14 or 15 were intermediates in these processes. However, in studies on a related cyclopropyl ketone, cis-1,7-dimethyltricyclo[4.4.0.$0^{2,6}$]decan-3-one, it was found that such unconjugated enones, which could be isolated in low yields, did not give mixtures of rearrangement products of the same composition as those which were obtained from the parent cyclopropyl ketone upon reaction with boron trifluoride in methylene chloride.[18]

If the 11,12-dehydro derivatives of 5 and 6 were to undergo rearrangements analogous to the parent saturated cyclopropyl ketones with Lewis acid catalysts, the natural products nootkatone and solavetivone, respectively, would be produced. Some preliminary experiments have indicated that the rearrangements of these unsaturated systems with boron trifluoride are also accompanied by extensive double bond isomerizations. Therefore, we are looking at reactions of these compounds with other electrophilic reagents which may be less prone to attack the isolated double bond.

Experimental Section[19]

1α,5α-Dimethyl-9α-isopropyl-tricyclo[4.4.0.0^{2,6}]decan-3-one (5)- A mixture 40 mg of 10% palladium-on-carbon and 4.0 mL of 95% ethanol was placed under hydrogen at 1 atm pressure and stirred until the uptake of hydrogen ceased. A solution of 0.217 g (0.0010 mol) of 1α,5-dimethyl-9α-(2-propen-2-yl)-tricyclo[4.4.0.0^{2,6}]dec-4-en-3-one (1) in 2.0 mL of 95% ethanol was injected into the mixture via a syringe and stirring was continued until the uptake of hydrogen ceased. The catalyst was removed by filtration and the solvent was removed in vacuo to give 0.200 g (91%) of 5 as a colorless oil: IR(CCl_4) 1716 cm^{-1} (cyclopropyl conj. C=O); NMR(CCl_4) δ 0.85 (d, J= 6 Hz, 6H, -CH(CH_3)$_2$), 1.14(d, J= 6.5 Hz, 3H, 5-CH_3) and 1.32(s, 3H, 1-CH_3); MS m/e(70eV) 220.1789(EMC = 220.1821).

Anal. Calcd for $C_{15}H_{24}O$:C, 81.76; H, 10.98. Found: C, 81.60; H, 10.96.

1α,5α-Dimethyl-8β-isopropyl-tricyclo[4.4.0.0^{2,6}]decan-3-one(7). A solution of 0.850 g (0.0039 mol) of the tricyclodecenone derivative 8 in 150 mL of 95% ethanol containing 150 mg of 10% palladium-on-carbon was shaken in a Parr hydrogenation apparatus under a hydrogen pressure of 25 psi for 3 h. The catalyst was removed by filtration and the solvent was removed in vacuo to give 0.780 g (92%) of 7: bp 120-130° C(0.1 mm); IR(CCl_4) 1719 cm^{-1} (cyclopropyl conj. C=O); NMR(CCl_4) δ 0.87(Mult., 6H, -CH(CH_3)$_2$), 1.14 (d, J = 7Hz, 3H, 5-CH_3), and 1.32(s, 3H, 1-CH_3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.70. H, 10.99.

1β,5α-Dimethyl-8β-isopropyl-tricyclo[4.4.0.0^{2,6}]decan-3-one (6) - n-Butyllithium (20.98 mL of a 2.24 M solution in hexane) was added slowly with stirring to a solution 6.59 mL (0.047 mol) of dry diisopropylamine and 50 mg of 2,2-bipyridyl in 200 mL dry tetrahydrofuran (THF) at 0°C under nitrogen. The reaction mixture was stirred for 30 min at 0°C and then cooled to -70°C. A solution of 8.8 g (0.043 mol) of 3,4,5,6,7,8-hexahydro-4aα-methyl-7β-isopropyl 2(4a H)-naphthalenone (9a)[10] in 50 mL of dry THF was then added dropwise with stirring and the mixture was stirred for an additional 30 min.

A solution of 7.99 g (0.026 mol) of diphenyldiselenide in 50 mL of dry THF was cooled in a dry ice-acetone bath for a few seconds and 1.32 mL (0.026 mol) of bromine was added with swirling. The solution of benzeneselenenyl bromide thus prepared was transferred to a dropping funnel and added rapidly to the solution of the kinetic dienolate of 9a. The mixture was stirred and allowed to warm to room temperature and 100 mL of a saturated solution of NH_4Cl was added. The mixture was then extracted with two 100-mL portions of ether and the ether extracts were washed with 150 mL each of 2% ice-cold hydrochloric acid, saturated $NaHCO_3$, and saturated NaCl. The solution was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. The residue was dissolved in 100 mL of methylene chloride and while the temperature of the mixture was maintained below 25°C a solution of 9.92 g of 30% hydrogen peroxide in 10 mL of water was added slowly with stirring. The mixture was stirred vigorously for an additional 1 h. Water (100 mL) was added and the layers were separated and the aqueous layer extracted with 100 mL of methylene chloride. The solvent from the combined methylene chloride extracts was removed in vacuo and the residue was dissolved in 100 mL ether. After filtration to remove insoluble benzeneselenenic acid, the solution was washed with 100 mL each of saturated $NaHCO_3$ and saturated NaCl.

The solution was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo to give 6.55 g (75%) of 5,6,7,8-tetrahydro-4aα-methyl-7β-isopropyl-2(4a H)-naphthalenone 9b: mp 83.5-84.3°C; IR(CCl_4) 1666(α,β-unsat'd C=O) and 1632 and 1608 cm^{-1} (conj. C=C); NMR (CCl_4) δ 0.79-0.98 (m, 6H, $-CH(\underline{CH_3})_2$), 1.30(s, 3H, 4a-CH_3), 5.95(d, J = 1.5 Hz 1 H, 1-H), 6.02(d of d , J = 1.5 and 9 Hz, 1H, 3-H), and 6.58 (d, J = 9 Hz, 1H, 4-H); MS m/e (70eV) 204.1513 (EMC = 204.151).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.26; H, 9.88.

A solution of 1.0 g of dienone 9b in 100 mL of anhydrous dioxane was irradiated for 1 h with a 7-watt Hanau NK 20 low pressure mercury lamp. The mixture was stirred by passage of a stream of dry nitrogen through it during the entire irradiation period. The solvent was removed in vacuo. The combined photo-mixtures from three identical runs were chromotographed on 70 g of silicon gel. Elution with 12% ether-hexane

gave 1.26 g (42%) of 1β-methyl-8β-isopropyl-tricyclo[4.4.0.$0^{2,6}$]dec-4-en-3-one (10): bp 93-97°C (0.03 mm); IR 1702 cm^{-1} (C=O); NMR(CCl_4) δ 0.9(d, J = 6 Hz, 6H, $-CH(\underline{CH_3})_2$), 1.17 (s, 3H, 1-CH_3), 5.75 (d or d, J = 1 and 5.5 Hz, 1H, 4-H), and 7.18 (d of d, J = 1 and 5.5 Hz, 1H, 5-H).

Anal. Calcd for $C_{14}H_{20}O$. C, 82.30; H, 9.87: Found C, 82.27; H, 9.88.

The procedure of House and coworkers[12] was used for the conversion of 10 into 6. Methyllithium (15.22 mmol, 13.83 mL of a 1.1 M solution in ether) was added dropwise with stirring to a solution of 1.71 g (8.32 mmol) of $(CH_3)_2SCuBr$ in 15 mL of dimethyl sulfide and 15 mL of anhydrous ether under nitrogen while the temperature was maintained at 20-25°C. The addition of methyllithium was stopped just at the point when the last of the initially formed yellow precipitate of $(CH_3Cu)_n$ dissolved to form a pale yellow solution. To this solution was added 1.24 g (6.1 mmol) of tricyclodecenone 10 in 5 ml of ether and the resulting mixture from which $(CH_3Cu)_n$ separated was stirred at 25°C for 45 min. The reaction mixture was partitioned between ether and an aqueous solution (pH = 8) of NH_4Cl and NH_4OH. The ether layer was dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo to give 1.27 g (95%) of a pale yellow liquid. GLC analysis indicated that only one product was present. Distillation gave 6: bp 115 -125°C (0.1 mm); IR(CCl_4) 1726 and 1706 cm^{-1} (C=O); ^1H NMR(CCl_4) δ 0.85(d, J = 6 Hz, 6H, $-CH(\underline{CH_3})_2$), 1.13 (d, J = 7 Hz, 3H, 5-CH_3), and 1.15 (s, 3H, 1-CH_3); ^{13}C NMR($CDCl_3$) δ 43.9(C-1), 46.3(C-2), 212.6(C-3), 47.7(C-4), 39.3(C-5), 29.5(C-6), 35.6(C-7), 32.4(C-8), 28.0(C-9), 25.7(C-10), 31.4(C-11), 19.7(C-12 to C-15); MS m/e (70eV) 220.1884 (EMC = 220.1827.

Anal. Calcd for $C_{15}H_{24}O$. C, 81.76; H, 10.98. Found: C, 81.75; H, 11.00.

Reaction of Cyclopropyl Ketone 5 in Boron Trifluoride in Methylene Chloride. Boron trifluoride gas was passed into a solution of 0.107 g of 5 in 5 mL of dry methylene chloride until the solution was saturated. The mixture was then allowed to stand for 24 h at 25°C and poured into 15 mL of 5% aqueous $NaHCO_3$. After shaking the layers were separated and the aqueous phase was extracted with two 10-mL portions of methylene chloride. The combined organic extracts were washed with two 10-mL

portions of saturated NaCl and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give 0.097 g of a mixture of products. GLC analysis (column A)[19] of this mixture showed that it contained greater than 65% of 11,12-dihydronootkatone (11) and four other minor components each of which made up 10% or less of the total volatile material. The actual yield of 11 was determined to be 46% using pure (+)-nootkatone[13] as an internal standard. A portion of this mixture (80 mg) was chromatographed on 10 g of silica gel. Elution of the column with 20% ether-hexane 30 mg (37% from 5) of 11,12-dihydronootkatone. This sample showed identical spectral properties and GLC behavior to a sample of 11 which was prepared by reduction of the 11,12 double bond in authentic (+)-nootkatone[13] with hydrogen in the presence of tris(triphenylphosphine) rhodium chloride.[14]

Some of the fractions which were eluted from the column with 5% and 10% solutions of ether-hexane contained some of the minor components in partially purified form. One of these showed an IR (CCl_4) absorption at 1714 cm^{-1} (saturated C = O) and NMR(CCl_4) absorptions for a vinyl proton and a vinyl methyl group. This possibly was a mixture of unconjugated octalones derived from openings of the 2,6-bond in 5 followed by proton transfer from C-5 and C-7. Another fraction showed UV absorption at 232 nm and IR absorptions at 1710,1683, and 1600 cm^{-1} possibly attributable to a cyclopentenone derivative which could result from cleavage of the 1,6-bond in 5 followed by migration of the 7-methylene group to the 1-position.[8b] However, the quantities of these materials were insufficient to permit their purification and positive identification.

Reaction of Cyclopropyl Ketone 7 with Boron Trifluoride in Methylene Chloride. Cyclopropyl ketone 7 (200 mg) was reacted with boron trifluoride in 20 mL methylene chloride in the same manner as that described for 5. After workup of the reaction mixture in the usual way 184 mg of an oil which according to GLC analysis (column A)[19] was a 9:1 mixture of enone 12a and an unidentified minor component was obtained. An analytical sample was collected by GLC (column B).[19] It showed: IR(CCl_4) 1663 (α,β-unsat'd C=O) and 1610 cm^{-1} (conj. C=C); NMR(CCl_4) δ 0.85-0.97 (m, 9H, $-CH(CH_3)_2$

and 4-CH_3), 1.03(s, 3H, 4a-CH_3), and 5.58 (br.s, 1H, vinyl H); MS: m/e (70eV) 220.1751 (EMC = 220.1821).

The GLC behavior and spectral properties of the major rearrangement product of 7 were identical to those of a sample prepared from the corresponding dienone 12b[4] with an 11,12-double bond as follows: A solution of 75 mg tris(triphenylphosphine) rhodium chloride in 15 mL of benzene was placed under a hydrogen pressure of 1 atm and stirred until the uptake of hydrogen had ceased. Then a solution of 110 mg of dienone 12b in 2 mL of benzene was introduced and the solution was stirred under a hydrogen pressure of 1 atm until 1 equiv. of hydrogen was absorbed. After filtration of the product through a column the containing 5 g ammonia, ~60 mg of enone 12a was isolated as a colorless oil.

Reaction of Cyclopropyl Ketone 6 with Boron Trifluoride in Methylene Chloride. Cyclopropyl ketone 6 (450 mg) was reacted with a saturated solution of boron trifluoride in methylene chloride under the same conditions as those described above for 5 and 7. After workup of the product in the usual manner, 380 mg of a yellow oil was obtained. GLC analysis (column A)[19] of this material indicated that it contained on major component and two minor components in an 18:1:1 ratio. Preparative GLC (column B)[19] did not permit complete purification of the major component. However, perparative TLC using 0.5 mm silica gel plates and 20% ether-hexane as the eluent allowed the isolation of an analytical sample of 11,12-dihydrosolavetivone (13): UV (95% C_2H_5OH) 242 nm (ε6, 400); IR(CCl_4) 1670 (α,β-unsat'd C=O) and 1616 cm^{-1} (conj. C=C); ^1H NMR(CCl_4) δ 0.89-1.01 (mult., 9H -$CH(CH_3)_2$ and -$CHCH_3$), 1.89(d, J = 1.2 Hz, vinyl CH_3), and 5.62 (q, J = 1.2 Hz, 1H, vinyl H); ^{13}C NMR($CDCl_3$) δ 41.0(C-1), 47.2(C-2), 33.4(C-3), 34.2(C-4), 50.2(C-5), 1660.0(C-6), 124.8(C-7), 198.0(C-8), 42.8(C-9), 38.9(C-10), 32.1(C-11), 21.4 and 20.8(C-12 to C-14), 15.9(C-5); MS: m/e (70eV) 220.1813(EMC = 220.1821).

Anal. Calcd for $C_{15}H_{20}O$: C, 81.76; H, 10.98. Found: C, 81.83; H, 10.96.

The sample of 13 obtained above was identical in GLC and TLC behavior and spectral properties to a sample prepared by selective reduction of the 11,12 double

bond of (-)-solavetivone.[15] This reduction was performed as follows: A solution of 50 mg of tris(triphenylphosphine)rhodium chloride in 10 mL of benzene was placed under a hydrogen pressure of 1 atm and stirred until the uptake of hydrogen closed. Then a solution of 61 mg of (-)-solavetivone in 1 mL of benzene was introduced via a syringe and the solution was stirred under a hydrogen pressure of 1 atm until 1 equiv of hydrogen had been absorbed. The solution was then passed through a column containing 5 g of silica gel and the solvent was removed in vacuo to give 54 mg of crude 11,12-dehydrosolavetivone, (13). A pure sample of 13 was obtained by preparative TLC using 20% ether-hexane as the eluant.

References and Notes

(1) This investigation was supported in part by Public Health Service Grant No. CA 12193 from the National Cancer Institute and by Grant No. CHE7810044 from the National Science Foundation.

(2) For a recent review, see Marshall, J. A., Brady, S. F., and Andersen, N. H., Fortschr. Chem. Org. Naturst., 1974, 31, 283.

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(15) We are grateful to Dr. Donald M. Gunn (I.C.I., Ltd.) and Dr. James S. Roberts (University of Stirling) for supplying us with an authentic sample of (-)-solavetivone.

(16) Initially we felt that methyl migration might occur primarily to relieve the 1,3-interaction between the 1α-and 5α-methyl groups in 5. However, in preliminary experiments it was found that the 5-nor methyl derivative of 5[5a] also yields mainly an octalone derivative derived from methyl migration upon treatment with boron trifluoride in methylene chloride.

(17) The 5-nor methyl derivative of 6[5a] was also found to rearrange largely to the corresponding spiro ketone related to 13 upon reaction with boron trifluoride.

(18) Caine, D.; Chu, C.-Y.; Krueger, L. M.; and Gupton, G. T. III, unpublished work.

(19) Melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 infrared spectrophotometer. The ^{1}H NMR spectra were obtained on a Varian T-60 NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a Jeol Fourier transform spectrometer, Model PFT-100. The chemical shifts are expressed in δ values (ppm) relative to Me_4Si as an internal standard. Abbreviations s, d, t, q., and mult. refer to singlet, doublet, triplet, quartet, and multiplet, respectively. The ^{13}C chemical shift assignments were consistent with off-resonance decoupling experiments. The mass spectra were obtained with a Hitachi (Perkin-Elmer) Model RMU-7. Gas-liquid chromatography was carried out using a Perkin-Elmer 881 or an Aerograph A-90-P3 gas chromatograph. A 6ft X 0.125 in. aluminum column packed with 20% Carbowax 20M on acid washed Chromosorb W (Column A) was employed for analytical work and a 10 ft X 0.25 in. stainless steel column containing the same packing material (Column B) was used for preparative work. Microanalyses were obtained by Atlantic Microlab, Inc., Atlanta, Ga.

A CONVENIENT SYNTHESIS OF 2,2-DISUBSTITUTED 3(2H)-FURANONES[1]

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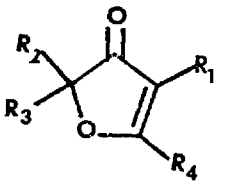
Summary: 2,2-Disubstituted 3(2H)-furanones can be prepared readily by 1,2-addition of organometallic compounds to γ,γ-disubstituted β-bromo-α,β-butenolides followed by treatment of the adducts with acid.

3(2H)-Furanones, which are valued for their aromas,[2] are useful synthetically as building blocks for muscarins[3] and tetronic acids[4] and as formyl ketone equivalents in photoannelation reactions.[5] Moreover, the findings that certain natural products such as jatrophone,[6] the eremantholides,[7] and geiparvarin[8] which exhibit anticancer activity contain a 3(2H)-furanone moiety have led to an increased interest in both the synthesis[9] and reactions[10] of these compounds.

Synthetic approaches to the 3(2H)-furanone system which vary in their degree of flexibility have appeared in the literature.[3,11] One of the general approaches to the synthesis of these compounds involves formation and acid-catalyzed cyclization of appropriate γ-hydroxy-β-dicarbonyl systems (2).[9,11c,d,g-j] It occurred to us that α,β-butenolides such as 4, having appropriate substituents at the β-carbon, should undergo 1,2-addition of organometallic reagents to yield masked γ-hydroxy-β-dicarbonyl compounds (3) which should be capable of undergoing hydrolysis and acid-catalyzed cyclization to the corresponding 3(2H)-furanones (1) possibly via intermediates such as 2.



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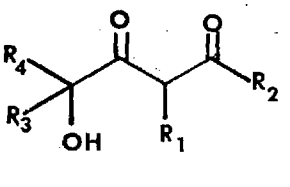
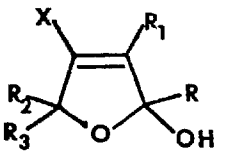


2

a. $R_1=R_2=R_3=R_4=CH_3$
b. $R_1=R_4=CH_3, R_3R_2=(CH_2)_5$
c. $R_1=H, R_2=R_3=CH_3, R_4=Ph$
d. $R_1=H, R_2=R_3=R_4=CH_3$
e. $R_1=H, R_2R_3=(CH_2)_5, R_4=CH_3$



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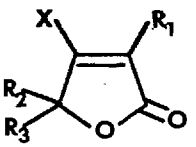

4

a. $R_1=R_2=R_3=CH_3$, X=Br
b. $R_1=CH_3, R_2R_3=(CH_2)_5$, X=Br
c. $R_1=H, R_2=R_3=CH_3$, X=Br
d. $R_1=H, R_2R_3=(CH_2)_5$, X=Br
e. $R_1=CH_3, R_3=H, R_2=$ i-Pr, X=Br

Various α,β-butenolides containing dialkylamino,[12] phenylthio,[13] or chloro[14] substituents at the β-position have been recently reported in the literature and appeared to be potentially useful candidates for the sesquence described above. However, we have found that lithium E-3-bromo-3-lithiopropenoate and its 2-methyl derivative, which can be obtained by treatment of the corresponding E-bromoacids with 2 equiv of n-butyllithium in ether or tetrahydrofuran at -70°C,[15] undergo facile addition to both aliphatic aldehydes and ketones[16] to give the corresponding γ-substituted β-bromobutenolides. Compounds 4a-e were prepared in yields in the 50-80% range by this method and their readily availability made them attractive precursors for the desired 3(2H)-furanones.

Benetti and coworkers have reported that β-alkyl substituted butenolides undergo 1,2-addition of 2 equiv. of Grignard or organolithium reagents to yield unsaturated 1,4-diols.[17] However, by carrying out inverse addition of phenyl- or methyllithium or methylmagnesium bromide to solutions of bromobutenolides 4a-e in ether at -25° it was possible to limit 1,2-addition to only 1 equiv. of the organometallic reagent and obtain, after acidification, adducts of the type 3. These adducts were not purified but were converted directly into 2,2-disubstituted furanones 1 by treatment with 20% aqueous sulfuric acid containing methanol as a cosolvent at room temperature for 14 h. The results of these runs are shown in the Table. The yields of products ranged from 47-76%. In the cases where relatively low yields were obtained, no improvement was observed when milder conditions applicable to the hydrolysis of vinyl halides[18] were employed.

The exact pathway for the conversions of the butenolide adducts 3 into the 3(2H)-furanones 1 is not known. An open chain γ-hydroxy-β-bromo-α,β-unsaturated ketone which may be in equilibrium with 3, may undergo hydrolysis of the vinyl halide to give a γ-hydroxy-β-dicarbonyl compound (2) which cyclizes to 1, or the hydroxyl group in 3 may undergo acid-catalyzed allylic rearrangement to the carbon atom bearing bromine followed by loss of hydrogen bromide.

When the γ-isopropyl butenolide 4e was reacted with 1 equiv. of methyllithium and the product subjected to hydrolysis as described above, 3-bromo-2-isopropyl-5-methylfuran was the only product obtained.[19] Thus the above sequence appears to be applicable to the synthesis 2,2-disubstituted 3(2H)-furanones only. However, it does offer remarkable flexibility particularly with regard to the substituents which may be introduced at the 2 and 5 positions.

Table. Preparation of 2,2-Disubstituted 3(2H)-Furanones (1) by Addition of Organometallic Reagents to β-Bromobutenolides Followed by Acid Hydrolysis.

Butenolide	Organometallic Reagent	3(2H)-Furanone[a]	Yield (%)	Ref.
4a	CH_3Li	1a	56	-
4b	CH_3Li	1b	76	-
	CH_3MgI	1b	67	-
4c	PhLi	1c	71	4,20
	CH_3Li	1d	47	11i
4d	CH_3Li	1e	70	11j

a. All of the 3(2H)-furanones exhibited the expected UV, IR, NMR (^1H and ^{13}C), and mass spectral properties. All new compounds gave elemental analyses which were correct to within ±0.3%.

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15. The conversion of E-3-bromo-2-methylpropenoic acid into lithium E-3-bromo-3-lithio-2-methylpropenoate by treatment with 2 equiv. of t-butyllithium in THF at low temperature has been reported (Aberhart, D. J.; Tann, C.-H. J. Chem. Soc., Perkin I, 1979, 939).

16. Although several β-lithio propenoic acid derivatives having heteroatoms at the β-position having been prepared and reacted with certain carbonyl compounds,[12,13] no examples of additions of reagents of this type to aliphatic ketones have been reported.

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FINAL PROJECT REPORT
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PART I–PROJECT IDENTIFICATION INFORMATION

1. Institution and Address	2. NSF Program	3. NSF Award Number
Georgia Institute of Technology Atlanta, Georgia 30332	Syn. organic & Nat'l Prod.	CHE 7810044
	4. Award Period From 1/12/78 To 5/31/82	5. Cumulative Award Amount 82,531*

6. Project Title

Synthetic Studies on Sesquiterpenoids

(*includes 12,151 supplement support)

PART II–SUMMARY OF COMPLETED PROJECT *(FOR PUBLIC USE)*

This summary briefly describes progress on the total synthesis of several sesquiterpene stress metabolites. The tricyclic compound (-)-phytuberin was totally synthesized from (-)-carone by stereospecific construction of a spirobutenolide intermediate derived from a tetrahydrocarvone derivative having a protected hydroxymethyl at C-2 an benzyloxy group at C-7; and, after removal of the hydroxyl-protecting groups, generation of the dihydro- and tetrahydrofuran rings of the natural product in one step. In connection with this project, the preparation and reactions of various lithium β-lithioacrylates was investigated. Reactions of these reagents with various carbonyl compounds (saturated and unsaturated ketones and aldehydes) provided a simple route to a variety of butenolides, including the natural product umbelactone. Butanolides were prepared in a similar way using lithium β-lithiopropionate and some of its derivatives. A new route to 3(2H)-furanones from β-bromo-butenolides was also developed.

An approach to the spirocyclic sesquiterpenes solavetivone and lubimin which involved spiroalkylation of 5-methylcyclohex-2-enone at C-6 with a γ,β'-disubstituted tiglate ester was explored. However, despite considerable effort on this project, we have been unable to synthesize an appropriate spiroalkylating agent in an acceptable yield. Solavetivone was prepared by acid-catalyzed rearrangement of a tricyclodecanone derivative.

A 6/6-fused β,γ-unsaturated acid with the carboxyl group in an angular position which appeared to be a logical precursor of the norsesquiterpene rishitin has been synthesized stereospecifically. However, attempts to decarboxylate this acid with rearrangement of the double bond have failed thus far. Other methods of carrying out this transformation are being explored.

PART III–TECHNICAL INFORMATION *(FOR PROGRAM MANAGEMENT USES)*

1. ITEM *(Check appropriate blocks)*	NONE	ATTACHED	PREVIOUSLY FURNISHED	TO BE FURNISHED SEPARATELY TO PROGRAM	
				Check (✓)	Approx. Date
a. Abstracts of Theses	X				
b. Publication Citations		X			
c. Data on Scientific Collaborators		X			
d. Information on Inventions	X				
e. Technical Description of Project and Results		X			
f. Other *(specify)* N/A					

2. Principal Investigator/Project Director Name *(Typed)*	3. Principal Investigator/Project Director Signature	4. Date
Drury S. Caine III		June 30, 1982

Form Approved OMB No. 99R

ATTACHMENTS:

Part III.

a. None

b. Publications:

"Acid-Catalyzed Rearrangements of Cyclopropyl Ketones Related to Eudesmane", D. Caine; S. L. Graham; and T. T. Vora, J. Org. Chem., 45, 3798 (1980).

"The Synthesis of Substituted α,β-Butenolides from γ-Hydroxy-α,β-Acetylenic Esters", D. Caine and T. L. Smith, Jr., Synthetic Communications, 10, 751 (1980).

"A Convenient Synthesis of 2,2-Disubstituted 3(2H)-Furanones", D. Caine and W. D. Samuels, Tetrahedron Lett., 4057 (1980).

"A Convenient Stereospecific Synthesis of (-)-Phytuberin from (-)-2-Carone, D. Caine and T. L. Smith, Jr. J. Am. Chem. Soc., 102, 7568 (1980).

"The Synthesis of (±)-Umbelactone", D. Caine, A. S. Frosbese, and V. Ukachukwu, submitted for publication, J. Org. Chem.

c. Scientific Collaborators:

Dr. Homer A. Smith, Jr. Professor
Ms. Candice J. McCloskey, Graduate Student
Mr. Everett Crews, Graduate Student
Mr. Charles R. Harrison, Graduate Student
Mr. Russell Patera, Graduate Student
Mr. Troy L. Smith, Jr. Graduate Student

d. Information of Inventions:

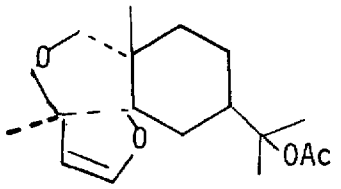
None

e. Project Description and Results (Period Covered 12/1/78 - 5/31/82):

The Synthesis of Phytuberin

A convenient, stereospecific synthesis of (-)-phytuberin (1) from (-)-2-carone has been completed recently.[1] (See attached reprint.) The synthesis required seven steps and the overall yield of the natural product was ~11%. It involved three stages: (1) stereospecific alkylation of the lithuim enolate of carone with chloromethylbenzyl ether and acid-catalyzed opening of the three-membered ring with benzyl alcohol to give a cyclohexanone derivative with a protected 1-hydroxymethyl group and a protected 4-hydroxyisopropyl group trans; (2) stereospectic generation of a β-methyl spirobutenolide by axial addition of lithuim propiolate to the carbonyl group of the cyclohexanone

derivative followed by 1,4-addition of lithuim dimethylcuprate to the γ-hydroxyacetylenic ester; (3) and, after deprotection of the hydroxyl groups, formation of the tetrahydro- and dihydrofuran ring in one step by reaction of the butenolide diol with diisobutylaluminuim hydride. In connection with this work it was found that β-methyl-α,β-butenolides could be prepared by conjugate addition of lithium dimethylcuprate to γ-hydroxy-acetylenic esters followed by acidification; β-methyl-α-allyl-α,β-butenolides were obtained if the intermediate cuprate adduct was treated with an allyl halide prior to acidification.[2] (See attached reprint.) Lithium Z-β-lithioacrylates, which are useful reagents for the direct synthesis of α,β-butenolides from ketones,[3] were not satisfactory for use in the synthesis of phytuberin because the stereochemical mode of the addition to an appropriate cyclohexanone derivative was incorrect.[1]



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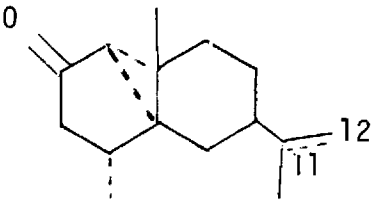

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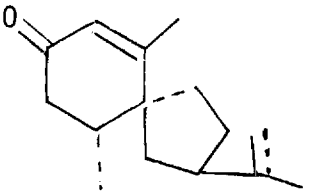

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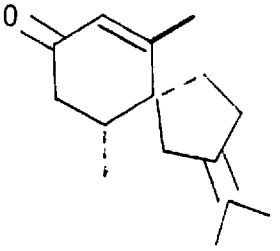

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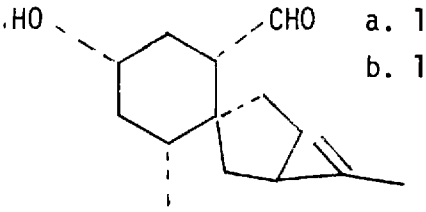


5

a. 11,12-bond sat'd

b. 11,12-bond unsat'd

Synthetic Approaches to Solavetivone and Lubimin

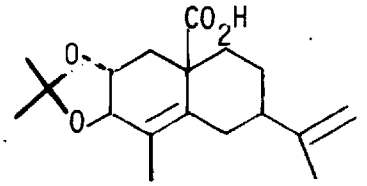
It has been found that the optically active tricyclodecanone derivative 2a undergoes rearrangement with BF_3 to produce (-)-11,12-dihydrosolavetivone (3a) in good yield.[4] (See attached reprint.) A ca. 1:1 mixture of (-)-solavetivone (3b) and 10-epi-β-vetivone (4) was obtained in about 60% yield when the unsaturated tricyclic ketone 2b was treated with BF_3 under carefully controlled conditions. We are hopeful that a Lewis acid catalyst which will promote rearrangement of 2b without isomerization of the double bond can be found.

A considerable amount of effort was devoted to the synthesis of a spiroalkylating agent which could be reacted with the 6-enolate of 5-methylcyclohex-2-enone to provide a spirocyclic intermediate suitable for conversion into solavetivone on lubimin (5). Ethyl γ,β'-dibromotiglate was prepared by a literature procedure, but we were unable to effect a clean separation of this compound from the isomeric monobromo tiglic esters which are produced as by products. Other attempts to prepare an appropriately substituted γ,β'-disubstituted tiglate ester by free radical chlorination of ethyl tiglate with t-butylhypochlorite and Wittig reactions involving various substituted aldehydes and phosphonuim salts failed.

Synthetic Approach to Rishitin

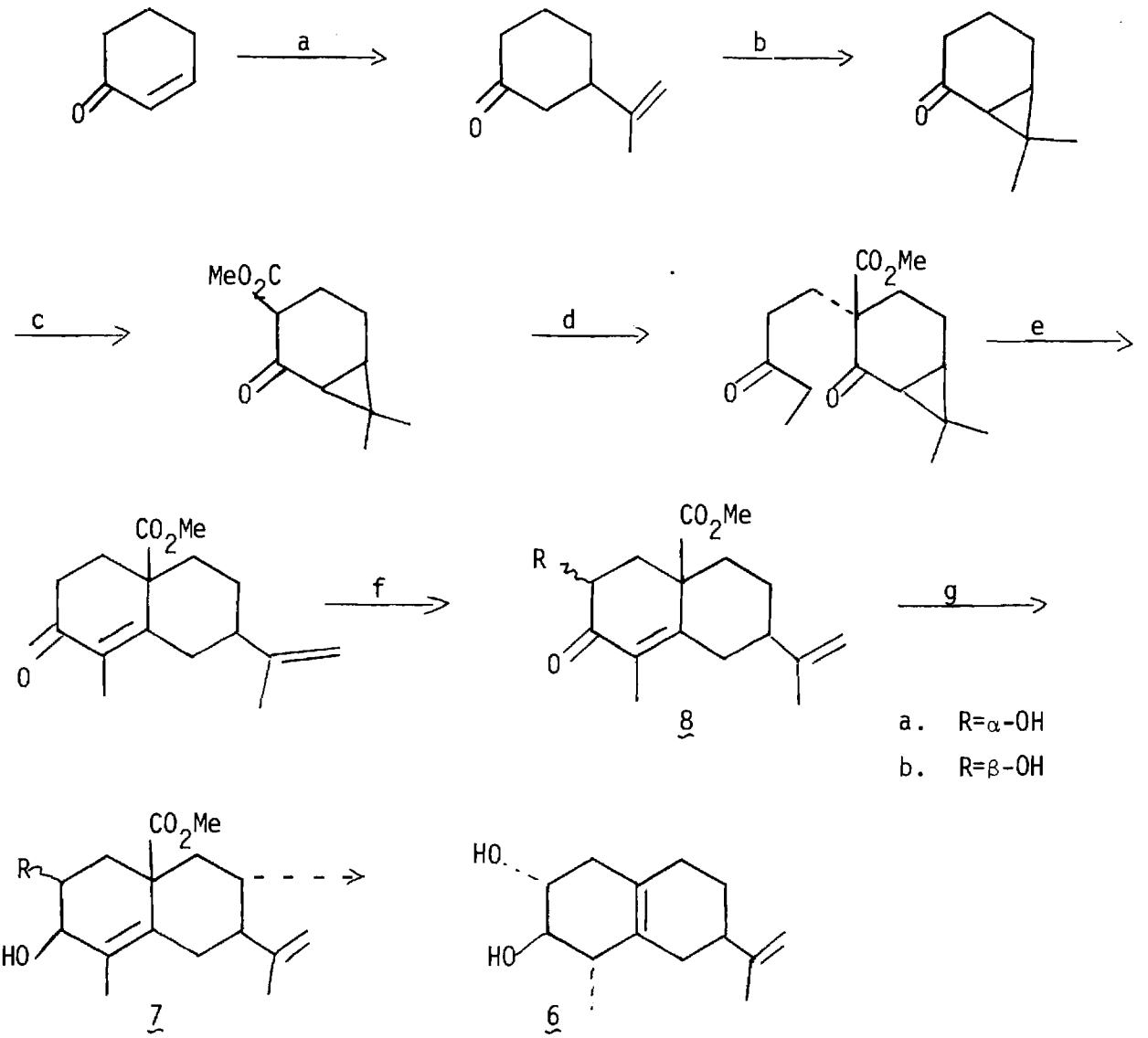
Scheme 1 shows an approach which we have investigated in an effort to synthesize racemic rishitin (6). A mixture of diols 7a and 7b was obtained by reduction of a ca. 50:50 mixture of hydroxy enones 8a and 8b with $LiAlH(Ot\text{-}Bu)_3$ in THF. However, we have been unable to isolate the pure diol 7a, the precursor of rishitin, in pure form by chromatographic methods.

Our intention was to produce the natural product 6 by converting 7a into its acetonide derivative, cleaving the methyl ester with LiI in collidine, decarboxylating the β,γ-unsaturated acid with a copper catalyst and removing the acetonide group. In order to determine if this approach was feasible the model acetonide derivative 9 was synthesized as shown in Scheme 2. Reaction of this compound with CuI in collidine gave primarily decomposition products. However, the ester group could be hydrolyzed to give the acid 10 with aqueous sodium hydroxide. When the acid was heated with copper powder a mixture of products believed to be the tetralin derivative 11 and the acetonide 12 with an unrearranged double bond was produced. The fact that the acid 10 underwent decarboxylative elimination indicates that in order to carry out a successful decarboxylation in this kind of bicyclic system the double bond must reside in the B ring. Therefore we are attempting to prepare the unsaturated acid 13 and will study its conversion to (±)-rishitin (6).



13

Scheme 1

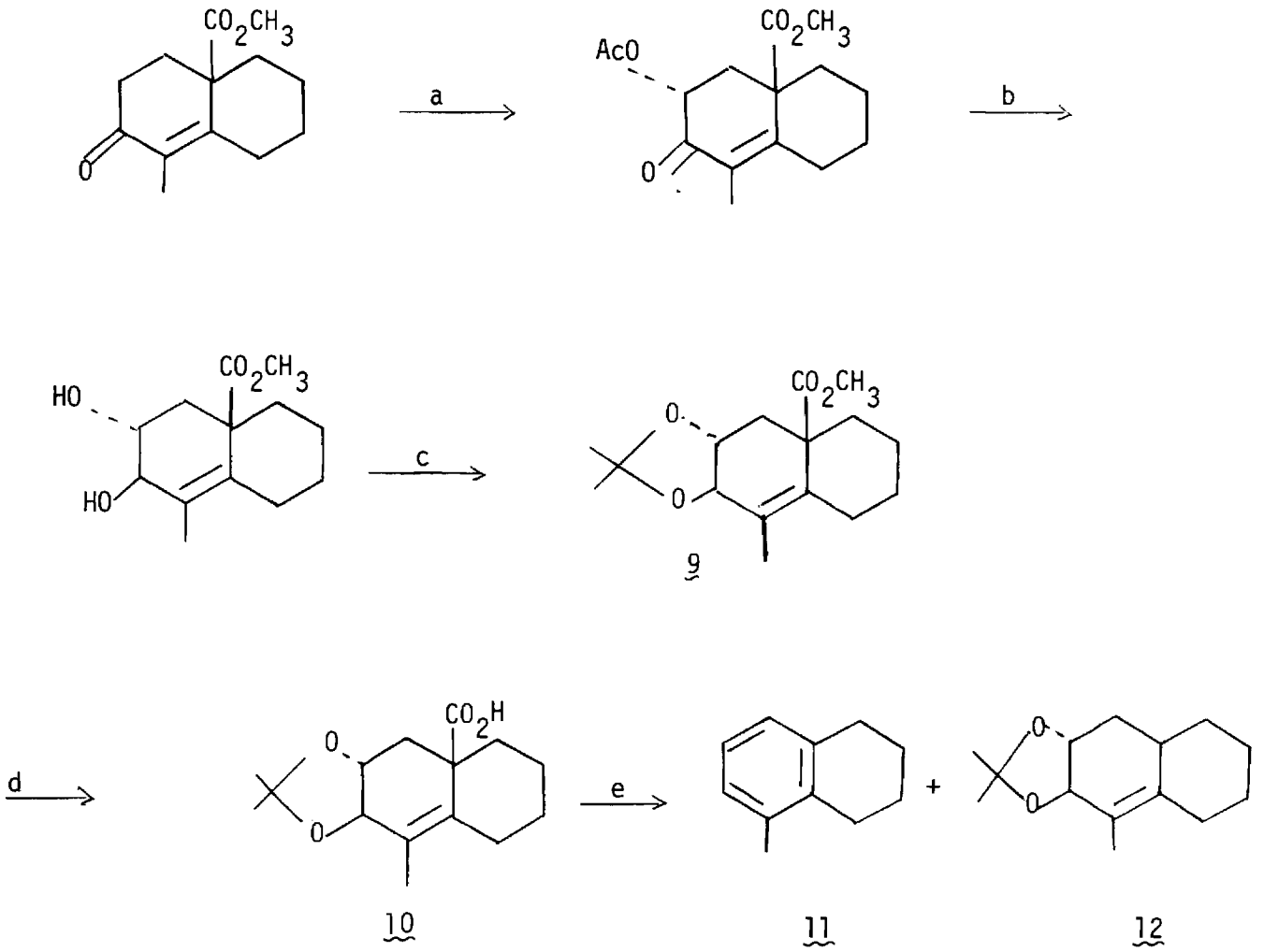


a. R=α-OH
b. R=β-OH

a. R=α-OH
b. R=β-OH
c. R = H

(a) $CH_3C(MgBr)=CH_2$, Cu(I)Br; (b) 1. HCl, $AlCl_3$; 2. KOH; (c) $(MeO)_2CO$, KH; (d) $CH_3CH_2COCH=CH_2$, KOH, Et_2O; (e) 1. HCl, EtOH, 2. NaOAc; (f) 1. LDA, THF, -78°; 2. TMSCl; 3. m-$ClC_6H_4CO_3H$; 4. H_3O^+; (g) LialH(Ot-Bu)$_3$, THF.

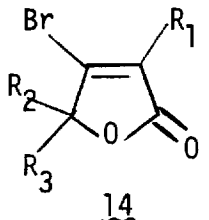
Scheme 2



a. $Pb(OAc)_4$, PhH; b. $LialH(Ot\text{-}Bu)_3$, THF; c. acetone, $HClO_4$(trace;
d. NaOH, H_2O; e. Cu powder, quinoline, heat.

Synthetic Approaches to α,β-Butenolides and Related Compounds Using Lithium Z-β-Lithioacrylates

Several β-bromo-α,β-butenolides of the type 14 have been obtained by addition of lithium β-bromo-β-lithioacrylates 15 to saturated and unsaturated ketones and saturated and aromatic aldehydes. β-Lithio-β-methoxyacrylates such as 16 were found to cause polymerization of aliphatic ketones rather than undergoing nucleophilic addition. However, 16 underwent addition to benzaldehyde in low yield. Uda and coworkers[5] have reported similar behavior for the methyl ester related to 16b. However, Miyata and Schmidt[6] have found that the methyl ester related to 16a undergoes addition to both saturated and unsaturated ketones. β-Bromobutenolides (14) proved to be useful intermediates for the synthesis of 2,2-disubstituted 3(2H)-furanones such as 17. This conversion involved 1,2-addition of an organometallic reagent (R_4M) to the carbonyl group followed by acid treatment.[7] (See attached reprint.) We hope to use the methodology developed in connection with the synthesis of compounds such as 17 to accomplish a total synthesis of the heliangolide ciliarin.



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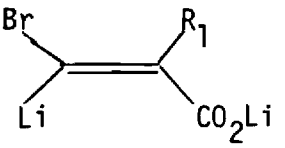

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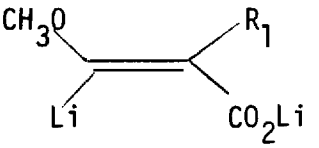

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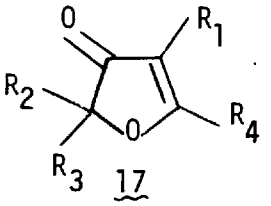
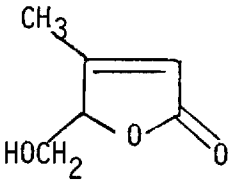
a. = R_1=H; b. R_1=CH_3



17

Work on the synthesis of the naturally occurring α-hydroxymethylbutenolide (±)-umbelactone (18) has been completed and a manuscript submitted for publication (see attached preprint). Two routes to 18 were developed. Both of these proceeded via the butenolide 19 having the hydroxyl group protected as the benzyl ether. A one-pot route to 19 involved addition of the lithiocarboxylate 20[3] to benzyoxyacetaldehyde and acidification while a two-step approach involved addition of the bromolithiocarboxylate 15a to the same aldehyde, acidification, and treatment of the bromobutenolide product with lithuim dimethylcuprate. The benzyl group was removed from 19 by catalytic hydrogenation.

We reported earlier (see project report for period 12/1/78-3/31/81) that the antibiotic lepichlorin (21) had been prepared by reaction of the lithiocarboxylate 22 with chloroacetyl chloride. However, efforts to repeat this experiment have failed. In spite of this we are still hopeful that proper conditions for a one-pot synthesis of 21 can be found. Lithiocarboxylate 22 was found to react with benzyloxyacetaldehyde to give after removal of the benzyl protecting the γ-hydroxymethylbutenolide 23 which has been converted into lepiochlorin by Donaubauer and McMorris[8] in three steps.



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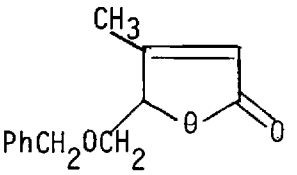

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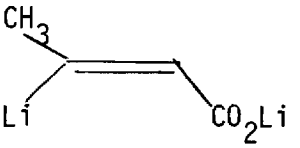

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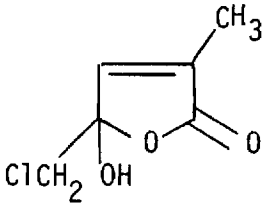

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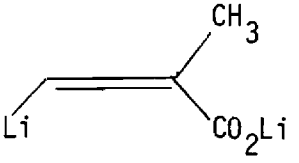

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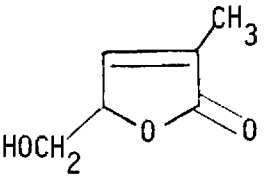
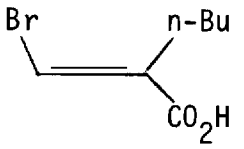


23

The α-n-butyl-β-bromoacrylic acid derivative 24 was prepared in the hope that the corresponding dilithio derivative could be reacted with tribromoacetaldehyde to give β-bromobutenolide 25 which would be convertible into the fimbrolide antibiotic 26[9] upon base treatment. However, it was observed that tribromoacetaldehyde served as a source of positive bromine when reacted with the β-lithioacrylate 15b and gave rise to β,β-dibromomethacrylic acid. Therefore this approach to 26 was abandoned.



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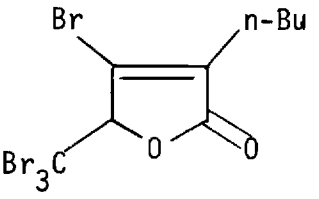

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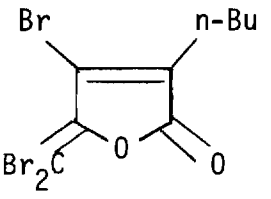

26

The reactions of dilithio acrylates such as 15, 20, and 22 with electrophilic reagents other than aldehydes or ketones are still being explored in order to determine the general synthetic utility of these reagents.

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2. Caine, D.; Smith, T. L., Jr. Syn. Commun., 1980, 751.

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8. A seven step synthesis of 21 was reported recently, see Donaubauer, J. R.; McMorris, T. C. Tetrahedron Lett., 1980, 2771.

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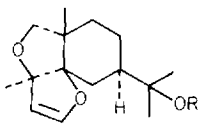
CHE 7810044

Reprinted from the Journal of the American Chemical Society, **1980,** *102,* 7568.

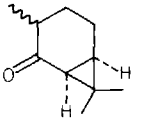
A Convenient, Stereospecific Synthesis of (–)-Phytuberin from (–)-2-Carone[1]

Sir:

\Phytuberin (**1a**) is a sesquiterpene stress metabolite which has been isolated from fungal-infected potato tubers by Coxon and co-workers.[2] Its structure was established by spectroscopic methods and by an X-ray crystallographic structure determination on its 2,3-dihydro derivative. A lengthy biogenetic-like synthesis of **1a** from α-cyperone, which established the absolute stereochemistry of the compound, was reported recently by Masamune and co-workers.[3,4] We wish to report a convenient, seven-step synthesis of **1a** from (–)-2-carone (**2**) which allowed preparation



1a, R = Ac
b, R = H



2

of the natural product in 11% overall yield.

The cyclohexanone derivative **3** was obtained in a highly stereospecific manner. Alkylation of the lithium 2,3-enolate of **2** prepared under thermodynamic conditions by using lithium di-

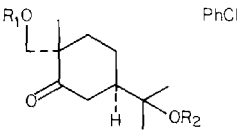
(1) This research was supported by a grant (NSF 7810044) from the National Science Foundation for which we are grateful.

(2) Coxon, D. T.; Price, K. R.; Howard, B.; Curtis, R. F. *J. Chem. Soc., Perkin Trans. 1* **1977**, 53.

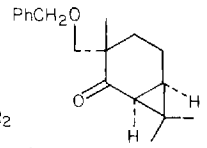
(3) Murai, A.; Ono, M.; Abiko, A.; Masamune, T. *J. Am. Chem. Soc.* **1978**, *100*, 7751.

(4) For the proposed biogenetic pathway to phytuberin, see Stossel, A.; Stothers, J. B.; Ward, E. W. B. *Can. J. Chem.* **1978**, *56*, 645.

isopropylamide (LDA) as the base in tetrahydrofuran (THF)[5] with chloromethyl benzyl ether gave the bicyclic ketone **4**[6] [65% yield; bp 120–126 °C (0.05 mm); $[\alpha]^{24}_D$ −93.4° (*c* 1.15, EtOH); IR (CCl_4) 1692 cm^{-1} (C=O); NMR (CCl_4) δ 0.91 (s, 3 H), 1.02 (s, 3 H), 1.10 (s, 3 H), 3.17 and 3.49 (AB q, *J* = 8.6 Hz, 2 H, $OCH_2C\lessgtr$), 4.42 (s, 2 H, $C_6H_5CH_2O$–), 7.23 (s, 5 H, C_6H_5)] as a single product. The cyclopropane ring in **4** was readily cleaved with aqueous acid to give **3a**. However, to avoid having to protect



3a, $R_1 = CH_2Ph$; $R_2 = H$
b, $R_1 = R_2 = CH_2Ph$



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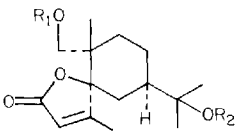
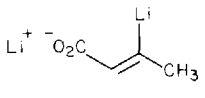


5a, $R_1 = R_2 = CH_2Ph$
b, $R_1 = R_2 = H$



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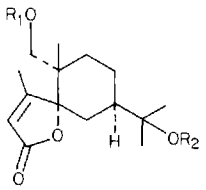
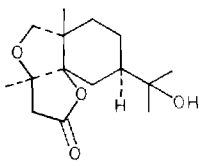


7a, $R_1 = R_2 = CH_2Ph$
b, $R_1 = R_2 = H$



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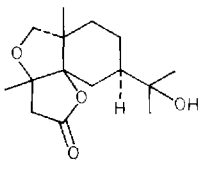

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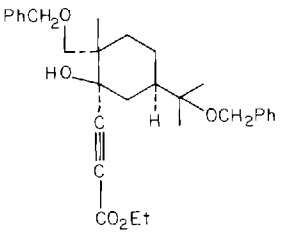

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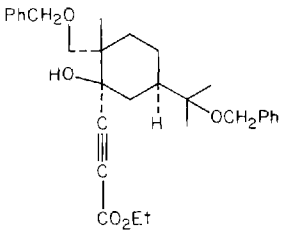

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the tertiary hydroxy group in a separate step, ketone **4** was treated with benzyl alcohol containing a catalytic amount of *p*-toluenesulfonic acid to give directly the dibenzyl derivative **3b**[6] [85% yield; $[\alpha]^{24}_D$ +30° (c 0.75, EtOH); IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 1.07 (s, 3 H), 1.25 (s, 6 H), 3.17 and 3.39 (ABq, *J* = 9.2 Hz, 2 H, $-OCH_2C\lessgtr$), 4.35 (s, 2 H, $C_6H_5CH_2O$–), 4.44 (s, 2 H, $C_6H_5CH_2O$–), 7.21 (s, 10 H, 2 C_6H_5's)].

We hoped to utilize methodology analogous to that which was reported recently for a direct conversion of ketone **3b** into the β-methyl spirobutenolide **5a**.[7] Thus, **3b** was reacted with the β-lithioacrylate derivative **6** (prepared by treatment of (*Z*)-3-bromobutenoic acid with 2 equiv of *n*-butyllithium in ether at −78 °C) under the conditions described previously for the conversion of ketones into butenolides.[7] This led to the formation of a ~12:88 mixture of the isomeric spirobutenolides **5a** and **7a** in 45–51% yield. The isomers which were separated by chromatography on silica gel exhibited the following spectral properties. **5a**:[6] [IR (CCl_4) 1755 (α,β-unsaturated γ-lactone C=O), 1637 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 1.09 (s, 3 H), 1.19 (s, 6 H), 2.08 (d, *J* = 1.6 Hz, 3 H), 3.18 and 3.41 (AB q, *J* = 9.0 Hz, 2 H), 4.45 (s, 2H), 4.61 (s, 5 H), 7.22 (s, 5 H), 7.27 (s, 5 H). **7a**:[6] IR (CCl_4) 1764 (C=O), 1637 cm^{-1} (C=C); NMR (CCl_4) δ 1.22 (s, 6 H), 1.27 (s, 3 H), 1.98 (d, *J* = 1.8 Hz, 3 H), 2.96 and 3.27 (AB q, *J* = 9.0 Hz, 2 H), 4.25 (s, 2 H), 4.35 (s, 2 H), 5.43 (q, *J* = 1.8 Hz, 1 H), 7.17 (s, 10 H).

Hydrogenation of the minor isomer **5a** in 95% ethanol containing 10% Pd(C) allowed quantitative removal of the benzyl protecting groups without reduction of the conjugated double bond to give the diol **5b**. When **5b** was allowed to stand on basic alumina[8] for 1 h and then eluted with 50% ether–hexane, deacetylphytuberin lactone **8**, which showed spectral properties identical with those of an authentic sample,[2,9] was isolated in 88% yield. Application of a similar sequence to the major butenolide led via **7b** to the tricyclic hydroxylactone **9**[6] [mp 61–62 °C; IR (CCl_4) 3620, 3480 (OH), 1772 (C=O), 1382, 1368, 1117, 1040, 1017, 906 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (s, 9 H), 1.40 (s, 3 H), 2.52 and 2.82 (AB q, *J* = 18 Hz, 2 H), 3.63 (s, 2 H)]. Since the addition of the vinyllithium reagent **6** to the carbonyl group in **3b** occurred predominantly from the undesired equatorial direction, it was clear that a method which would lead to the butenolide **5a** stereoselectively would have to be sought.

It was felt that the addition of a relatively small carbanionic species such as acetylide ion to the carbonyl group in **3b** might occur predominately from the axial direction.[10] In a model study it was found that addition of lithium carboxyethylacetylide[11] to a 4-*tert*-butylcyclohexanone occurred almost exclusively in the axial manner; furthermore, it was observed that the resulting γ-hydroxy acetylenic ester was converted into the corresponding anti β-methyl spirobutenolide by reaction with 2 equiv of lithium dimethylcuprate.[12] Thus it appeared that an analogous two-step process might be applicable to the **3b** → **5a** conversion. Indeed, the first step proceeded readily and the γ-hydroxyacetylenic ester **10**[6] [92% yield; $[\alpha]^{24}_D$ +22° (*c* 1.18, EtOH); IR (CCl_4) 3495 (OH), 2225 (C≡C), 1715 cm^{-1} (C=O); NMR (CCl_4) δ 1.08 (s, 3 H), 1.21 (s, 6 H), 1.30 (t, *J* = 7.4 Hz, 3 H), 3.19 and 3.79 (AB q, *J* = 8.9 Hz, 2 H), 4.18 (q, *J* = 7.4 Hz, 2 H), 4.40 (s, 2 H), 4.56 (s, 2 H), 7.22 (s, 5 H), 7.28 (s, 5 H)] formed by axial addition was obtained when **3b** was reacted with lithium (carboxyethyl)-acetylide in THF at −78 °C for 1.0 h. The stereochemistry of **10** was confirmed by the subsequent transformations. None of the isomeric γ-hydroxy ester which could have resulted from equatorial addition to **3b** was isolated.

Considerable difficulty was encountered in finding proper conditions to effect the **10** → **5a** conversion. When **10** was treated with 2 equiv of lithium dimethylcuprate in THF at ~−10 °C for 3 h under the same conditions which were used to convert the adduct of lithium (carboxyethyl)acetylide and 4-*tert*-butylcyclohexanone into the corresponding *anti*-β-methyl spirobutenolide,[12] only unchanged starting material was recovered. When the cuprate addition was run in THF at 0–25 °C by using 2–10 equiv of reagent, the tertiary alcohol **11**[6] [mp 97.5–98.5 °C; IR(CCl_4) 3620, 3520 (OH), 2230 cm^{-1} (C≡C); NMR (CCl_4) δ 1.10 (s, 3 H), 1.20 (s, 6 H), 1.43 (s, 6 H), 3.16 and 3.78 (AB q, *J* = 8.6 Hz, 2 H), 4.40 (s, 2 H), 4.53 (s, 2 H), 7.23 (s, 5 H), 7.35 (s 5 H)], which resulted from 1,2 addition of the cuprate to the carboxyethyl group, was the only product isolated. When the reaction was carried out at temperatures below −10 °C for extended reaction times using 2 equiv of lithium dimethylcuprate in ether, mixtures of the butenolides **5a**, the acetylenic diol **11**, and the starting material were isolated. However, best results were obtained when **10** was reacted with 1 equiv of lithium dimethylcuprate in ether at −24 °C for 84 h. This led to the formation of a ~3:1:1 mixture of **5a**, **11**, and **10**.[13] Chroma-

(5) Treatment of **2** with LDA in THF at −78 °C under kinetic control followed by addition of methyl chloromethyl ether or benzyl chloromethyl ether gave C-1 rather than C-3 alkylation products.

(6) All new compounds for which spectral data are reported gave correct combustion analyses and/or exact mass data.

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tography of the mixture on silica gel allowed the isolation of **5a** in 60% yield, based on unrecovered starting material.

In order to form the tetrahydro and dihydrofuran rings in phytuberin, diol **5b**, which was prepared by hydrogenolysis of the benzyl groups in **5a**, was reacted with 3.5 equiv of DIBAL-H (−40 °C, 1.0 h; 0 °C, 0.5 H), as described for the reduction of the related formylspirobutenolide.[3] Workup of the mixture with 2 N NaOH gave deacetylphytuberin (**1b**), $[\alpha]^{24}_D$ −34.6° (*c* 0.1, EtOH), in 63% yield. This material exhibited identical spectral properties with those reported previously.[2,3] Acetylation of **1b** (Ac_2O, Et_3N, catalytic amount of 4-*N*,*N*-dimethylaminopyridine[14]) gave 71% of (−)-phytuberin (**1a**), $[\alpha]^{24}_D$ −34.0 ° (*c* 0.25, EtOH), having IR and NMR spectral properties and TLC behavior identical with those of an authentic sample.[9]

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(13) Since the best yield of the butenolide was obtained when 1 equiv of lithium dimethylcuprate was used, it is possible that the conjugate addition reaction was effected primarily via the mixed methylalkoxycuprate derived from reaction of lithium dimethylcuprate with the hydroxy group in **10**. For examples of conjugate additions using mixed alkylalkoxycuprates, see Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788.

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THE SYNTHESIS OF SUBSTITUTED α,β-BUTENOLIDES FROM γ-HYDROXY-α,β-ACETYLENIC ESTERS

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The α,β-butenolide ring system is found in a number of physiologically important natural products[2] and there has been recent interest in the development of methods of synthesis of compounds of this type.[3] It is well known that α,β-unsubstituted butenolides may be prepared by catalytic hydrogenation of γ-hydroxy acetylenic acids.[4,5b] Recently, an excellent route of γ-hydroxy acetylenic esters which involves the addition of the lithium acetylide salts of propiolic esters to aldehydes[5] and ketones[6] has become available. We have carried out the addition of ethyl lithiopropiolate (1) to cyclohexanone (2) and 4-t-butylcyclohexanone (3) and wish to report the conversion of these adducts into corresponding β-methyl or β-methyl-α-allyl-α,β-butenolides.

1-[2-(Carboethoxy)ethynyl]cyclohexanone (4), the adduct of 1 and 2, was prepared according to the procedure described by Schlessinger

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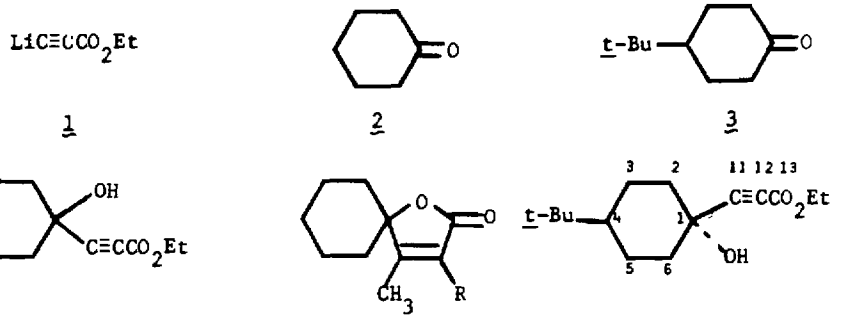
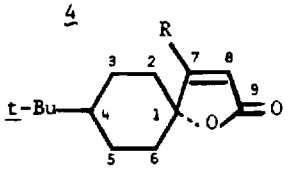
and coworkers.[5b,c] This procedure was similar to that described for Midland and coworkers,[6] except that lithium diisopropylamide (LDA) was used as the base for the preparation of 1. The conjugate addition of lithium dialkylcuprates to α,β-acetylenic esters provides a method of sterospecific synthesis of tri- and/or tetra-substituted olefins.[7] Treatment of adduct 4 with 2 equiv. of lithium dimethylcuprate, prepared from reaction of methyllithium with the cuprous bromide-dimethylsulfide complex,[8] in anhydrous ether for 16 h at -78°C followed by acidification with hydrochloric acid gave the known β-methylbutenolide 5a[9] in 84% yield.[10]

Additions of lithium dialkylcuprates to acelytenic esters are presumed to proceed via α-carboalkoxy vinyl copper intermediates.[7] Such species have been reacted with allylic halides to yield α-substituted-α,β-unsaturated esters.[11] Thus, when dry hexamethylphosphoramide (HMPA) (~10% by volume) followed by 4.3 equiv. of allyl bromide was added to the reaction mixture obtained from addition of lithium dimethylcuprate to 4, the α-allyl-β-methyl-α,β-butenolide 5b was obtained in 71% yield after acidification with hydrochloric acid and distillation.

Additions of metal acetylides to 4-t-butylcyclohexanone occur mainly from the axial direction with respect to the carbonyl group.[12] Upon reaction of 1 with 3 the acetylenic carbinol 6 was obtained in 84% yield. The stereochemistry of the adduct 6 was established by converting it into the butenolide 7a by catalytic hydrogenation in 95% ethanol containing quinoline using 5% palladium on barium sulfate as the catalyst. Butenolide 7a was found to be

identical to the minor product of addition of lithium Z-β-lithioacrylate to 3.[3e] Treatment of 6 with lithium dimethylcuprate





7 a. R=H
b. R=CH_3

according to the procedure described by Carlson and coworkers[7c] gave α-methyl-α,β-butenolide 7b in 76% yield.[10] Methodology analogous to that described above should be generally useful for the synthesis of other β-alkyl or β-alkyl-α-allyl-α,β-butenolides.

EXPERIMENTAL SECTION[13]

1-[2-(Carboethoxy)-ethynyl]cyclohexanol(4)[5b,c] - Dry diisopropylamine (2.86 ml, 20.4 mmol) was added to 25 ml of dry tetrahydrofuran (THF) and the solution was cooled to -10°C and treated with 8.68 ml of 2.35 M n-BuLi in hexane. The mixture was stirred for 15 min and then cooled to -78°C. Ethyl propiolate (2.00 g, 20.4 mmol) was then added slowly, the reaction mixture was stirred for 1 h, and then 2.00 g (20.4 mmol) of cyclohexanone in 5 ml of dry THF was added dropwise. The mixture was stirred

overnight (~16 h) at -78°C and 40 ml of 1:1 conc hydrochloric acid-water was added. The mixture was then diluted with 100 ml water and extracted with four 50 ml portions of ether. The combined ethereal extracts were washed with 50 ml of saturated $NaHCO_3$ and 50 ml of saturated NaCl. The solution was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. Distillation of the residue gave 3.21 g (83%) of the ethynyl carbinol 4;[6] bp 112-113° (bath temperature)/ 0.18 mm; IR (CCl_4) 3610, 3470, 2230, 1718 cm^{-1}; ^1H NMR (CCl_4) δ 1.33 (t, 3H, J = 7.2 Hz), 4.27 (q, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 68.9 (s), 38.8 (t), 22.7 (t), 24.9 (t), 38.8 (t), 75.6 (s), 90.3 (s), 153.1 (s), 61.8 (t), 14.0 (q); MS (70 eV) m/e 196(1), 125(100).

1-Oxa-4-methylspiro[4.5]dec-3-en-2-one (5a)[10] - Methyllithium (3.06 ml, 1.4 M in ether) was added dropwide to a stirred slurry of $CuBr \cdot S(CH_3)_2$ in 15 ml of anhydrous ether at 0°C. The mixture was allowed to stir for 15 min, cooled to -78°C, and 0.200 g (1.2 mmol) of the ethylnyl carbinol 4 in 2 ml of anhydrous ether was added. The mixture was stirred for 14.0 h at -78°C and allowed to warm to room temperature and stirred for an additional 4.0 h. It was then poured into ~50 ml of cold 1 N hydrochloric acid and stirred for 1.0 h. The aqueous phase was extracted with four 25 ml poritions of ether and the combined etheral extracts were washed with 50 ml of saturated $NaHCO_3$ followed by 50 ml of saturated NaCl and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was distilled to yield 0.144 g (85%) of the butenolide 5a:[9,3e] bp 110-115°C (bath temperature)/0.2 mm; mp 49-51°C; IR (CCl_4) 1761 and 1648 cm^{-1}; ^1H NMR (CCl_4) δ 2.00 (d, 3H, J = 1.8 Hz) and 5.59 (q, 1H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$)[14] δ

88.5 (s), 33.1 (t), 21.8 (t), 24.5 (t), 21.8 (t), 33.1 (t), 171.5 (s) 114.9 (d), 172.8 (s), and 13.2 (q).

1-Oxa-4-methyl-3(1-prop-2-enyl)spiro[4.5]dec-3-en-2-one (5b) - Methyllithium (6.48 ml, 1.40 M in ether) was added dropwise to a stirred slurry of 1.07 g (5.19 mmol) of $CuBr \cdot S(CH_3)_2$ in 25 ml of anhydrous ether at -6°C. The mixture was allowed to stir for 30 min, cooled to -78°C, and 0.424 g (2.16 mmol) of 4 in 3 ml of anhydrous ether was added. The mixture was stirred for 12.0 h at -78° and allowed to warm to room temperature and stirred for an additional 4 h. The mixture was cooled to 0°C and 2.5 ml of anhydrous HMPA and 1.1 g (9.3 mmol) of allylbromide in 3 ml of anhydrous ether was added. The mixture was stirred for 1.0 h at 0°C and worked up as described above to yield 0.315 g (71%) of the butenolide 5b; bp 118-122°C (bath temperature)/0.1 mm; IR (CCl_4), 3075, 1760, 1675, and 1635 cm^{-1}; ^1H NMR (CCl_4) δ 1.95 (s, 3H), 2.93 (broad d, 2H, J = 6.0 Hz); 5.00 (dm, 2H), and 5.83 (ddt, 1H, J = 9.5, 18.0, and 6.0 Hz); ^{13}C NMR ($CDCl_3$)[14] δ 86.9 (s), 33.3 (t), 21.8 (t), 24.5 (t), 21.8 (t), 33.3 (t), 165.0 (s), 123.0 (s), 172.2 (s), 11.2 (q), 27.3 (t), 132.9 (d), 115.2 (t); MS (70 eV) m/e 206.1303 (calc 206.1307); 79 (100). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.70; H, 8.82.

trans-4-t-Butyl-1-[2-(carboethoxy)-ethynyl]cyclohexanol (6)[5b] - Dry diisopropylamine (1.96 g, 19.4 mmol) was added to 20 ml of anhydrous THF and the solution was cooled to -10°C and treated with a 8.78 ml of 2.21 M n-BuLi in hexane. The mixture was stirred for 15 min and cooled to -78°C. Ethyl propiolate (1.91 g, 19.4 mmol)

was then added slowly, the mixture was stirred for 1 hr, and 3.00 g (19.4 mmol) of 4-t-butylcyclohexanone in 5 ml of anhydrous THF was added. The mixture was stirred 16 h at -78°C and treated with 50 ml of 1:1 conc. hydrochloric acid-water. Work up of the mixture as described for 4 gave 4.10 g (94%) of the ethynyl carbinol 6; mp 54-55°C; IR (CCl_4) 3610, 3420, 2230 and 1721 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (s, 9H), 1.30 (t, 3H, J = 7.4 Hz), 4.16 (q, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$)[14] δ 68.9 (s), 39.5 (t), 24.6 (t), 46.8 (d), 24.6 (t), 39.5 (t), 32.1 (s), 27.4 (q), 27.4 (q), 27.4 (q), 76.4 (s), 89.9 (s), 153.0 (s), 61.6 (t), 14.0 (q); MS (70 eV) m/e 252.1735 (Calc for $C_{15}H_{24}O_3$ 252.1725).

1-Oxa-7-t-butylspiro[4.5]dec-3-en-2-one 7a:[5b] - A mixture of 1.15 g (4.56 mmol) of the ethynyl carbinol 6 in 5 ml of 95% ethanol containing 56 μL of quinoline and 58 mg of 5% $Pd/BaSO_4$ was stirred under a hydrogen atmosphere at 25° until the theoretical quantity of hydrogen had been taken up. The mixture was then filtered to remove the catalyst and the solvent was removed under reduced pressure. The residue was poured into 50 ml of cold 10% hydrochloric acid and stirred for 2 h. Ether (100 ml) was added and after shaking the mixture the layers were separated. The aqueous layer was then extracted with two 50 ml portions of ether and the combined ethereal extracts were washed with 50 ml saturated $NaHCO_3$, 50 ml of saturated NaCl, and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave 0.868 g (91%) of the butenolide: IR (CCl_4) 1771 and 1608 cm^{-1}; NMR (CCl_4) δ 0.93 (s, 9H), 5.97 (d,

1H, J = 5.8 Hz), 7.80 (d, 1H, J = 5.8 Hz); MS (70 eV) 208 (56), 151 (100). Butenolide 7a exhibited identical GLC behavior to the minor butenolide component prepared by addition of lithium Z-β-lithioacylate to 4-t-butylcyclohexanone.[3e]

1-Oxa-4-methyl-7-t-butylspiro[4.5]dec-3-en-2-one (7b)[7c] - A slurry of freshly purified CuI in 40 ml of anhydrous THF was stirred and cooled to -10°C and 12.7 ml of methyllithium (1.31 M in ether) was added slowly. The mixture was stirred for 30 min at -10° and a solution of 1.00 g (3.96 mmol) of ethynyl carbinol 6 in 5 ml of anhydrous THF was added. The mixture was stirred at -10°C for 3 h and poured into 100 ml of 10% hydrochloric acid and stirred vigorously for 1.0 h. It was then extracted with four 50 ml portions of ether and the combined ethereal extracts were washed with two 50 ml portions of saturated $NaHCO_3$, one 50 ml portion of saturated NaCl, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give 0.70 g (76%) of the butenolide 7b; mp 87-88°C; IR (CCl_4) 1762 and 1635 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (s, 9H), 2.20 (d, 3H, J = 1.4 Hz), and 5.57 (q, 1H, J = 1.4 Hz); ^{13}C NMR ($CDCl_3$)[14] δ 88.3 (s), 34.0 (t), 23.5 (t), 44.9 (d), 23.5 (t), 34.0 (t), 171.2 (s), 115.8 (d), 172.5 (s), 16.6 (q), 32.3 (s), 27.4 (q), 27.4 (q), and 27.4 (q); MS (70 eV) m/e 222.1628 (calc 222.1620); 57 (100).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.83; H, 10.00.

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10. While the reaction of $LiCuMe_2$ with 6 could be carried out in THF at -5° to 0°C with only a small amount of 1,2-addition (≈10%), it was found that under similar conditions the adduct 4 gave a mixture of 1,4- and 1,2-addition products along with the starting material in 60:30:10 ratio. To achieve only 1,4-addition to 4, the reaction was carried out in ether at -78°C overnight.

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Acid-Catalyzed Rearrangements of Cyclopropyl Ketones Related to Eudesmane[1]

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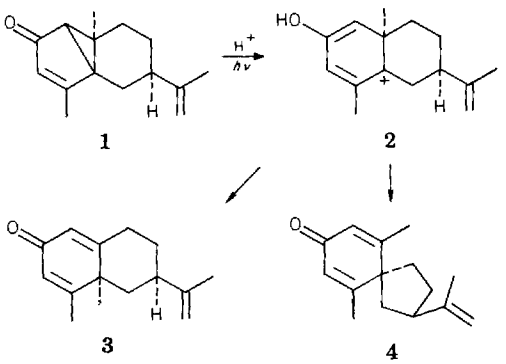
Tricyclodecanones 5–7 have been synthesized. Upon reaction with the Lewis acid boron trifluoride in methylene chloride these compounds underwent opening of the cyclopropane ring and rearrangement of the carbon skeleton. Cyclopropyl ketones 5 and 7, which are stereochemically related to 10-epieudesmane, gave 11,12-dihydronootkatone (11) and the octalone derivative **12a**, respectively, as the major products upon treatment with boron trifluoride. In each case these products apparently arose via opening of the internal (2,6) bond of the cyclopropane ring followed by a 1,2-shift of the 1-methyl group to C-6. On the other hand, cyclopropyl ketone 6, which is stereochemically related to eudesmane, gave 11,12-dihydrosolavetivone (13) as the major product upon treatment with boron trifluoride. This spirocyclic enone apparently was produced by opening of the internal bond of the cyclopropane and a 1,2-shift of the 10-methylene group to C-6.

The currently accepted biogenetic pathways for the formation of nootkatone (eremophilane) or spirovetivane sesquiterpenes involve 1,2-methyl or -methylene migrations in bicyclic carbonium ions related to eudesmane.[2] In recent years there has been a considerable amount of interest in the duplication of rearrangements of these types in the laboratory.[3,4] In the preceding paper we reported that nootkatane and spirovetivane sesquiterpenes may be interconverted by photochemical pathways.[4] In this work bicyclic or spirocyclic intermediates containing a cross-conjugated cyclohexadienone chromophore in ring A were converted into the corresponding tricyclodecenone derivatives (lumiproducts) by irradiation in dioxane at 254 nm. These lumiproducts were then irradiated in aqueous acetic acid with greater than 300-nm wavelength ultraviolet light to produce dienone products with the appropiate sesquiterpene skeletons.

The types of photochemical rearrangements described above can be illustrated by using the tricyclodecenone derivative 1, which is related to 10-epieudesmane. Light-induced cleavage of the internal bond of the cyclopropane ring in 1 apparently leads to the bicyclic carbonium ion 2 which may undergo 1,2-methyl migration to produce dehydronootkatone (3) or 1,2-methylene migration to produce anhydro-β-rotunol (4). The latter pathway is significantly favored since the initial ratio of 3 to 4 was 1:5.6.[4]



1 2 3 4

Conjugated cyclopropyl ketones are known to react readily with a variety of electrophilic reagents. Upon treatment with (1) halogen acids in ethanol or acetic acid they undergo ring opening to yield γ-halo ketones,[5] (2) with protic or Lewis acid catalysts in nucleophilic solvents they yield ketones derived from ring opening followed by proton transfer or incorporation of the solvent at the γ-position,[5b,6] and (3) in systems where structural features permit, the ring-opening process may be accompanied by olefin or aryl participation[7] or rearrangement of the carbon skeleton[8] when Lewis acids in aprotic solvents are used as the electrophilic reagents.

The latter results indicated that reactions of tricyclodecanone derivatives related to 1 with Lewis acid catalysts in aprotic solvents might lead to rearrangement products having a nootkatone and/or a spirovetivane ring skeleton. Therefore, we have synthesized the diastereomeric tricyclodecanones 5[9] and 6, which have a carbon skeleton related to eudesmane, and the tricyclodecanone 7, having a 9α- rather than an 8β-isopropyl group, and have investigated the reactions of these compounds with boron trifluoride in methylene chloride.

Cyclopropyl ketone 5 was readily obtained from dienone 1[4] by catalytic hydrogenation over palladium on carbon in ethanol. Cyclopropyl ketone 7 was prepared in a similar manner by catalytic hydrogenation of the corresponding dienone 8.[4] Examination of models of both 1 and 8 clearly indicated that the β side of the 4,5 double bond was much less hindered than the α side. The stereochemistry of the 5-methyl groups in 5 and 7 was assigned on the basis of the assumption that hydrogen would add from the less hindered side of the double bond. These assignments were

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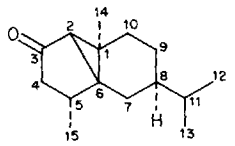
[Reprinted from the Journal of Organic Chemistry, **1980**, *45*, 3798.]



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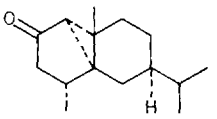

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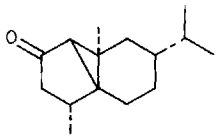
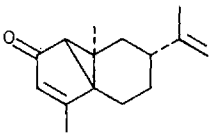


7

confirmed by the subsequent rearrangement reactions described below.

Cyclopropyl ketone **6** was prepared by conversion of the known enone **9a**[10] into the corresponding cross-conjugated dienone **9b** by the phenylselenylation–selenoxide elimination procedure,[11] photochemical rearrangement of **9b** to the tricyclodecenone **10** by irradiation with 254-nm ul-



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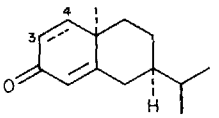
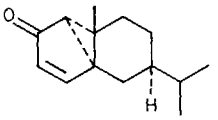


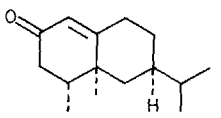
9a, 3,4-bond saturated
b, 3,4-bond unsaturated



10

traviolet light in anhydrous dioxane, and conjugate addition of lithium dimethylcuprate to the enone system, using the procedure of House and co-workers.[12] In the latter reaction a single product was obtained in ca. 95% yield. The 1β-methyl in **10** would provide a considerable amount of steric hindrance to the approach of the cuprate reagent from the β side of the 4,5 double bond. Thus it was assumed that the conjugate-addition product contained a 5α-methyl group, as indicated in **6**. This stereochemical assignment was supported by subsequent experiments.

Ketone **5** was allowed to react with a saturated solution of boron trifluoride in dry methylene chloride for 24 h at room temperature. GLC analysis of the reaction mixture indicated that essentially all of the starting material had been consumed and one major product which made up greater than 65% of the volatile compounds had been formed. The mixture also contained four minor components, but none of these amounted to as much as 10% of the total volatile material. The major product was isolated by chromatography on silica gel. Its spectral properties indicated that it was a bicyclic enone. These properties, as well as the GLC behavior of the product, were found to be identical with those of an authentic sample of 11,12-dihydronootkatone (**11**), which was prepared by selective hydrogenation of natural nootkatone[13] using the homogeneous catalyst tris(triphenylphosphine)rhodium chloride in benzene.[14]



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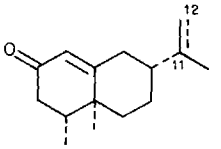

12a, 11,12-bond saturated
b, 11,12-bond unsaturated

The minor components of the reaction of **5** could not be isolated in sufficiently pure form to permit positive identification. However, examination of the spectral properties of partially purified materials indicated that a mixture of unconjugated bicyclic enones, resulting from cleavage of the 2,6-bond of the cyclopropane ring and proton transfer from C-5 and C-7, and a cyclopentenone derivative, resulting from cleavage of the 1,6-bond and migration of the 7-methylene group to C-1, probably were produced. Products of similar structures were observed to be formed in small amounts when a steriodal cyclopropyl ketone related to **5** was reacted with Lewis acids.[8b] No evidence for the formation of any spirocyclic enone which would result from concomitant cleavage of the 2,6-bond and migration of the 10-methylene group to C-6 was obtained.

Cyclopropyl ketone **7** was treated under the same conditions as those described for the isomer **5**. In this case GLC analysis indicated that only two products were formed in an ~9:1 ratio in ~80% yield. The major component was purified by preparative GLC. It exhibited identical GLC behavior and spectral properties with those of a sample of the enone **12a** which was prepared from dienone **12b**[4] by selective hydrogenation of the 11,12 double bond using tris(triphenylphosphine)rhodium chloride in benzene.[14] The minor component of the acid-catalyzed reaction of **7** was not identified. However, GLC and spectral evidence indicated that a spirocyclic product, i.e., 11,12-dihydrosolavetivone (**13**), which could have been formed by opening the 2,6-bond and migration of the 10-methylene group to C-6, was not produced.

The reaction of cyclopropyl ketone **6** with boron trifluoride was investigated next. When treated as described above it yielded one major product and two minor components in an 18:1:1 ratio by GLC. The yield of volatile products was ~80%. The major product was purified by preparative TLC. It exhibited identical spectral properties and chromatographic behavior (GLC and TLC) with an authentic sample of 11,12-dihydrosolavetivone (**13**) which was obtained by selective hydrogenation of the double bond in the isopropenyl group of (−)-solavetivone[15] using tris(triphenylphosphine)rhodium chloride in benzene. Insufficient quantities of the minor components of the reaction of **6** were available to permit identification.

The formation of 11,12-dihydronootkatone (**11**) from cyclopropyl ketone **5** involves cleavage of the internal (2,6) bond of the three-membered ring and migration of the 1-methyl group to C-6. In the relatively nonpolar solvent methylene chloride it is possible that the entire process

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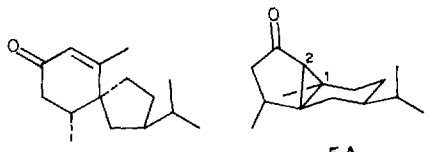
(12) House, H. O.; Chu, C. Y.; Wilkens, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

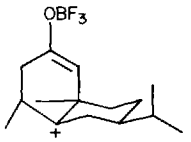
(13) We are grateful to Dr. Ben Clark of the Coca-Cola Company for a sample of pure (+)-nootkatone.

(14) (a) Huffman, J. W. *J. Org. Chem.* **1972**, *37*, 2736. (b) Odom, H. C.; Pinder, A. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2193.

(15) We are grateful to Dr. Donald M. Gunn (I.C.I., Ltd.) and Dr. James S. Roberts (University of Stirling) for supplying us with an authentic sample of (−)-solavetivone.

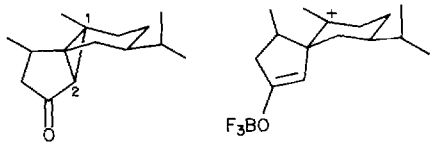


13 5A

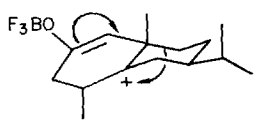


14

is concerted, since bond cleavage and bond formation can occur from the opposite sides of C-6. However, it may be formally represented as proceeding via a bicyclic carbonium ion intermediate. The most favorable conformation of ketone **5** would be expected to be **5A** in which the isopropyl group is equatorial to the six-membered ring. In **5** the external (1,2) bond of the cyclopropane ring overlaps more favorably than the internal bond with the π orbital of the carbonyl group. However, in **5A** cleavage of the 2,6-bond can occur in a diaxial manner, leading to a bicyclic carbonium ion in conformation **14** in which the enolized carbonyl function is axial with respect to the B ring.[6b] In this species, a transition state which allows for maximum orbital overlap during migration to C-6 appears to be much more easily achieved by the methyl group than the methylene group. The establishment of a conjugated enone system apparently provides a strong driving force for a rearrangement reaction as opposed to proton-transfer processes which would lead to unconjugated bicyclic enones.[16] However, as noted above, proton-transfer products were possibly produced in small quantities from **5**. The same conformational and electronic factors which are involved in the arrangement of **5** to **11** also seem to account for the formation of the octalone **12a** from the tricyclodecanone **7**. We were surprised to find that cyclopropyl ketone **6** gave primarily the spiro enone 11,12-dihydrosolavetivone (**13**) on reaction with boron trifluoride. The most favorable conformation of **6** should be as represented in **6A** in which opening of the external (1,2) bond could occur in a diaxial sense. Thus products formally arising from rearrangement via the spiro carbonium ion intermediate **15** were expected in this case.



6A 15



16

Indeed, we have observed that reaction of the 5-normethyl derivative of **6** with hydrogen bromide in acetic acid led mainly to a spirocyclic bromo ketone resulting from opening of the three-membered ring in the diaxial manner.[5a] (In contrast, the normethyl derivative of **5** gave exclusively a bicyclic bromo ketone, again by a pathway also involving cleavage of the ring in a diaxial manner.)[5a] However, it seems that spiro enone **13** would have to arise from migration of the 10-methylene group to C-6 in a bicyclic carbonium ion intermediate. It is possible that the spiro carbonium ion **15** is formed initially but rearranges to a bicyclic species with a conformation such as **16**, in which steric interaction between the methyl group at C-5 and the 7-methylene group is minimized and the 10-methylene group is favorably disposed for migration, faster than other reactions occur.[17] In the conversion of **6** into **13**, cleavage of the 2,6-cyclopropyl bond and formation of the new carbon–carbon bond by methylene migration must occur from the same side of C-6. Therefore, the possibility of a concerted methylene migration seems less likely here than in the systems in which methyl migration was observed.

The above mechanistic arguments are based upon the assumption that the reaction products were produced under kinetic control. The bicyclic and spirocyclic enones which were formed were shown to be stable under the reaction conditions. We cannot rule out the possibility that other undetected conjugated enones or bicyclic or spirocyclic unconjugated enones derived from proton-transfer reactions in carbonium ions such as **14** or **15** were intermediates in these processes. However, in studies on a related cyclopropyl ketone, *cis*-1,7-dimethyltricyclo[4.4.0.0^{2,6}]decan-3-one, it was found that such unconjugated enones, which could be isolated in low yields, did not give mixtures of rearrangement products of the same composition as those which were obtained from the parent cyclopropyl ketone upon reaction with boron trifluoride in methylene chloride.[18]

If the 11,12-dehydro derivatives of **5** and **6** were to undergo rearrangements analogous to the parent saturated cyclopropyl ketones with Lewis acid catalysts, the natural products nootkatone and solavetivone, respectively, would be produced. Some preliminary experiments have indicated that the rearrangements of these unsaturated systems with boron trifluoride are also accompanied by extensive double bond isomerizations. Therefore, we are looking at reactions of these compounds with other electrophilic reagents which may be less prone to attack the isolated double bond.

Experimental Section[19]

1α,5α-Dimethyl-9α-isopropyltricyclo[4.4.0.0^{2,6}]decan-3-one (5). A mixture 40 mg of 10% palladium on carbon and 4.0 mL of 95% ethanol was placed under hydrogen at 1-atm pressure and stirred until the uptake of hydrogen ceased. A solution of 0.217

(16) Initially we felt that methyl migration might occur primarily to relieve the 1,3-interaction between the 1α- and 5α-methyl groups in **5**. However, in preliminary experiments it was found that the 5-normethyl derivative of **5**[5a] also yields mainly an octalone derivative derived from methyl migration upon treatment with boron trifluoride in methylene chloride.

(17) The 5-normethyl derivative of **6**[5a] was also found to rearrange largely to the corresponding spiro ketone related to **13** upon reaction with boron trifluoride.

(18) Caine, D.; Chu, C.-Y.; Krueger, L. M.; Gupton, G. T., III, unpublished work.

(19) Melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 infrared spectrophotometer. The ^{1}H NMR spectra were obtained on a Varian T-60 NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL fourier transform spectrometer, Model PFT-100. The chemical shifts are expressed in δ values (parts per million) relative to Me_4Si as an internal standard. Abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. The ^{13}C chemical shift assignments were consistent with off-resonance decoupling experiments. The mass spectra were obtained with a Hitachi (Perkin-Elmer) Model RMU-7. Gas–liquid chromatography was carried out a Perkin-Elmer 881 or an Aerograph A-90-P3 gas chromatograph. A 6 ft × 0.125 in. aluminum column packed with 20% Carbowax 20M on acid-washed Chromosorb W (column A) was employed for analytical work and a 10 ft × 0.25 in. stainless-steel column containing the same packing material (column B) was used for preparative work. Microanalyses were obtained by Atlantic Microlab, Inc., Atlanta, GA.

g (0.0010 mol) of 1α,5-dimethyl-9α-(isopropenyl)tricyclo-[4.4.0.0^{2,8}]dec-4-en-3-one (1) in 2.0 mL of 95% ethanol was injected into the mixture via a syringe and stirring was continued until the uptake of hydrogen ceased. The catalyst was removed by filtration and the solvent was removed in vacuo to give 0.200 g (91%) of **5** as a colorless oil: IR (CCl_4) 1716 cm^{-1} (cyclopropyl conjugated C=O); NMR (CCl_4) δ 0.85 (d, J = 6 Hz, 6 H, CH-(CH_3)$_2$), 1.14 (d, J = 6.5 Hz, 3 H, 5-CH_3), 1.32 (s, 3 H, 1-CH_3); mass spectrum, m/e (70 eV) 220.1789 (calcd 220.1821).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.60; H, 10.96.

1α,5α-Dimethyl-8β-isopropyltricyclo[4.4.0.0^{2,6}]decan-3-one (7). A solution of 0.850 g (0.0039 mol) of the tricyclodecenone derivative **8** in 150 mL of 95% ethanol containing 150 mg of 10% palladium on carbon was shaken in a Parr hydrogenation apparatus under a hydrogen pressure of 25 psi for 3 h. The catalyst was removed by filtration and the solvent was removed in vacuo to give 0.780 g (92%) of **7**: bp 120–130 °C (0.1 mm); IR (CCl_4) 1719 cm^{-1} (cyclopropyl conjugated C=O); NMR (CCl_4) δ 0.87 (m, 6 H, CH(CH_3)$_2$), 1.14 (d, J = 7 Hz, 3 H, 5-CH_3), 1.32 (s, 3 H, 1-CH_3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.70; H, 10.99.

1β,5α-Dimethyl-8β-isopropyltricyclo[4.4.0.0^{2,6}]decan-3-one (6). n-Butyllithium (20.98 mL of a 2.24 M solution in hexane) was added slowly with stirring to a solution of 6.59 mL (0.047 mol) of dry diisopropylamine and 50 mg of 2,2-bipyridyl in 200 mL of dry tetrahydrofuran (THF) at 0 °C under nitrogen. The reaction mixture was stirred for 30 min at 0 °C and then cooled to −70 °C. A solution of 8.8 g (0.043 mol) of 3,4,5,6,7,8-hexahydro-4aα-methyl-7β-isopropyl-2(4aH)-naphthalenone (**9a**)[10] in 50 mL of dry THF was then added dropwise with stirring and the mixture was stirred for an additional 30 min.

A solution of 7.99 g (0.026 mol) of diphenyl diselenide in 50 mL of dry THF was cooled in a dry ice–acetone bath for a few seconds and 1.32 mL (0.026 mol) of bromine was added with swirling. The solution of benzeneselenenyl bromide thus prepared was transferred to a dropping funnel and added rapidly to the solution of the kinetic dienolate of **9a**. The mixture was stirred and allowed to warm to room temperature and 100 mL of a saturated solution of NH_4Cl was added. The mixture was then extracted with two 100-mL portions of ether and the ether extracts were washed with 150 mL each of 2% ice-cold hydrochloric acid, saturated $NaHCO_3$, and saturated NaCl. The solution was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. The residue was dissolved in 100 mL of methylene chloride and while the temperature of the mixture was maintained below 25 °C a solution of 9.92 g of 30% hydrogen peroxide in 10 mL of water was added slowly with stirring. The mixture was stirred vigorously for an additional 1 h. Water (100 mL) was added, the layers were separated, and the aqueous layer was extracted with 100 mL of methylene chloride. The solvent from the combined methylene chloride extracts was removed in vacuo and the residue was dissolved in 100 mL of ether. After filtration to remove insoluble benzeneselenenic acid, the solution was washed with 100 mL each of saturated $NaHCO_3$ and saturated NaCl.

The solution was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo to give 6.55 g (75%) of 5,6,7,8-tetrahydro-4aα-methyl-7β-isopropyl-2(4aH)-naphthalenone (**9b**): mp 83.5–84.3 °C; IR (CCl_4) 1666 (α,β-unsaturated C=O), 1632 and 1608 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 0.79–0.98 (m, 6 H, CH(CH_3)$_2$), 1.30 (s, 3 H, 4a-CH_3), 5.95 (d, J = 1.5 Hz, 1 H, 1-H), 6.02 (d of d, J = 1.5 and 9 Hz, 1 H, 3-H), 6.58 (d, J = 9 Hz, 1 H, 4-H); mass spectrum, m/e (70 eV) 204.1513 (calcd 204.151).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.26; H, 9.88.

A solution of 1.0 g of dienone **9b** in 100 mL of anhydrous dioxane was irradiated for 1 h with a 7-W Hanau NK 20 low-pressure mercury lamp. The mixture was stirred by passage of a stream of dry nitrogen through it during the entire irradiation period. The solvent was removed in vacuo. The combined photomixtures from three identical runs were chromatographed on 70 g of silica gel. Elution with 12% ether–hexane gave 1.26 g (42%) of 1β-methyl-8β-isopropyltricyclo[4.4.0.0^{2,6}]dec-4-en-3-one (**10**): bp 93–97 °C (0.03 mm); IR 1702 cm^{-1} (C=O); NMR (CCl_4) δ 0.9 (d, J = 6 Hz, 6 H, CH(CH_3)$_2$), 1.17 (s, 3 H, 1-CH_3), 5.75 (d of d, J = 1 and 5.5 Hz, 1 H, 4-H), 7.18 (d of d, J = 1 and 5.5 Hz, 1 H, 5-H).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.27; H, 9.88.

The procedure of House and co-workers[12] was used for the conversion of **10** into **6**. Methyllithium (15.22 mmol, 13.83 mL of a 1.1 M solution in ether) was added dropwise with stirring to a solution of 1.71 g (8.32 mmol) of $(CH_3)_2SCuBr$ in 15 mL of dimethyl sulfide and 15 mL of anhydrous ether under nitrogen while the temperature was maintained at 20–25 °C. The addition of methyllithium was stopped just at the point when the last of the initially formed yellow precipitate of $(CH_3Cu)_n$ dissolved to form a pale yellow solution. To this solution was added 1.24 g (6.1 mmol) of tricyclodecenone **10** in 5 mL of ether, and the resulting mixture, from which $(CH_3Cu)_n$ separated, was stirred at 25 °C for 45 min. The reaction mixture was partitioned between ether and an aqueous solution (pH 8) of NH_4Cl and NH_4OH. The ether layer was dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo to give 1.27 g (95%) of a pale yellow liquid. GLC analysis indicated that only one product was present. Distillation gave **6**: bp 115–125 °C (0.1 mm); IR (CCl_4) 1726 and 1706 cm^{-1} (C=O); ^{1}H NMR (CCl_4) δ 0.85 (d, J = 6 Hz, 6 H, CH(CH_3)$_2$), 1.13 (d, J = 7 Hz, 3 H, 5-CH_3), 1.15 (s, 3 H, 1-CH_3); ^{13}C NMR ($CDCl_3$) δ 43.9 (C-1), 46.3 (C-2), 212.6 (C-3), 47.7 (C-4), 39.3 (C-5), 29.5 (C-6), 35.6 (C-7), 32.4 (C-8), 28.0 (C-9), 25.7 (C-10), 31.4 (C-11), 19.7 (C-12 to C-15); mass spectrum, m/e (70 eV) 220.1884 (calcd 220.1827).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.75; H, 11.00.

Reaction of Cyclopropyl Ketone 5 with Boron Trifluoride in Methylene Chloride. Boron trifluoride gas was passed into a solution of 0.107 g of **5** in 5 mL of dry methylene chloride until the solution was saturated. The mixture was then allowed to stand for 24 h at 25 °C and poured into 15 mL of 5% aqueous $NaHCO_3$. After the mixture was shaken, the layers were separated and the aqueous phase was extracted with two 10-mL portions of methylene chloride. The combined organic extracts were washed with two 10-mL portions of saturated NaCl and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give 0.097 g of a mixture of products. GLC analysis (column A)[19] of this mixture showed that it contained greater than 65% 11,12-dihydronootkatone (**11**) and four other minor components each of which made up 10% or less of the total volatile material. The actual yield of **11** was determined to be 46%, using pure (+)-nootkatone[13] as an internal standard. A portion of this mixture (80 mg) was chromatographed on 10 g of silica gel. Elution of the column with 20% ether–hexane gave 30 mg (37% from **5**) of 11,12-dihydronootkatone. This sample showed identical spectral properties and GLC behavior with a sample of **11** which was prepared by reduction of the 11,12 double bond in authentic (+)-nootkatone[13] with hydrogen in the presence of tris(triphenylphosphine)rhodium chloride.[14]

Some of the fractions which were eluted from the column with 5% and 10% solutions of ether–hexane contained some of the minor components in partially purified form. One of these showed an IR (CCl_4) absorption at 1714 cm^{-1} (saturated C=O) and NMR (CCl_4) absorptions for a vinyl proton and a vinyl methyl group. This possibly was a mixture of unconjugated octalones derived from opening of the 2,6-bond in **5** followed by proton transfer from C-5 and C-7. Another fraction showed UV absorption at 232 nm and IR absorptions at 1710, 1683, and 1600 cm^{-1}, possibly attributable to a cyclopentenone derivative which could result from cleavage of the 1,6-bond in **5** followed by migration of the 7-methylene group to the 1-position.[8b] However, the quantities of these materials were insufficient to permit their purification and positive identification.

Reaction of Cyclopropyl Ketone 7 with Boron Trifluoride in Methylene Chloride. Cyclopropyl ketone **7** (200 mg) was reacted with boron trifluoride in 20 mL of methylene chloride in the same manner as that described for **5**. After workup of the reaction mixture in the usual way, 184 mg of an oil, which according to GLC analysis (column A)[19] was a 9:1 mixture of enone **12a** and an unidentified minor component, was obtained. An analytical sample was collected by GLC (column B):[19] IR (CCl_4) 1663 (α,β-unsaturated C=O), 1610 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 0.85–0.97 (m, 9 H, CH(CH_3)$_2$ and 4-CH_3), 1.03 (s, 3 H,

4a-CH_3), 5.58 (br s, 1 H, vinyl H); mass spectrum, m/e (70 eV) 220.1751 (calcd 220.1821).

The GLC behavior and spectral properties of the major rearrangement product of **7** were identical with those of a sample prepared from the corresponding dienone **12b**[4] with an 11,12 double bond as follows. A solution of 75 mg of tris(triphenylphosphine)rhodium chloride in 15 mL of benzene was placed under a hydrogen pressure of 1 atm and stirred until the uptake of hydrogen had ceased. Then a solution of 110 mg of dienone **12b** in 2 mL of benzene was introduced and the solution was stirred under a hydrogen pressure of 1 atm until 1 equiv of hydrogen was absorbed. After filtration of the product through a column the containing 5 g of ammonia, ~60 mg of enone **12a** was isolated as a colorless oil.

Reaction of Cyclopropyl Ketone 6 with Boron Trifluoride in Methylene Chloride. Cyclopropyl ketone **6** (450 mg) was reacted with a saturated solution of boron trifluoride in methylene chloride under the same conditions as those described above for **5** and **7**. After workup of the product in the usual manner, 380 mg of a yellow oil was obtained. GLC analysis (column A)[19] of this material indicated that it contained one major component and two minor components in an 18:1:1 ratio. Preparative GLC (column B)[19] did not permit complete purification of the major component. However, preparative TLC using 0.5-mm silica plates and 20% ether–hexane as the eluant allowed the isolation of an analytical sample of 11,12-dihydrosolavetivone (**13**): UV (95% C_2H_5OH) 242 nm (ϵ 6400); IR (CCl_4) 1670 (α,β-unsaturated C=O), 1616 cm^{-1} (conjugated C=C); ^1H NMR (CCl_4) δ 0.89–1.01 (m, 9 H, $CH(CH_3)_2$ and $CHCH_3$), 1.89 (d, J = 1.2 Hz, vinyl CH_3), and 5.62 (q, J = 1.2 Hz, 1 H, vinyl H); ^{13}C NMR ($CDCl_3$) δ 41.0 (C-1), 47.2 (C-2), 33.4 (C-3), 34.2 (C-4), 50.2 (C-5), 166.0 (C-6), 124.8 (C-7), 198.0 (C-8), 42.8 (C-9), 38.9 (C-10), 32.1 (C-11), 21.4 and 20.8 (C-12 to C-14), 15.9 (C-15); mass spectrum, m/e (70 eV) 220.1813 (calcd 220.1821).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.83; H, 10.96.

The sample of **13** obtained above was identical in GLC and TLC behavior and spectral properties with a sample prepared by selective reduction of the 11,12 double bond of (–)-solavetivone.[15] This reduction was performed as follows. A solution of 50 mg of tris(triphenylphosphine)rhodium chloride in 10 mL of benzene was placed under a hydrogen pressure of 1 atm and stirred until the uptake of hydrogen ceased. Then a solution of 61 mg of (–)-solavetivone in 1 mL of benzene was introduced via a syringe and the solution was stirred under a hydrogen pressure of 1 atm until 1 equiv of hydrogen had been absorbed. The solution was then passed through a column containing 5 g of silica gel and the solvent was removed in vacuo to give 54 mg of crude 11,12-dehydrosolavetivone (**13**). A pure sample of **13** was obtained by preparative TLC using 20% ether–hexane as the eluant.

Registry No. **1**, 74431-66-6; **5**, 61187-65-3; **6**, 74431-17-7; **7**, 74397-88-9; **8**, 53768-19-7; **9a**, 16735-08-3; **9b**, 69035-61-6; **10**, 69044-04-8; **11**, 70267-57-1; **12a**, 74397-89-0; **12b**, 74397-90-3; **13**, 74431-18-8.

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A CONVENIENT SYNTHESIS OF 2,2-DISUBSTITUTED 3(2H)-FURANONES[1]

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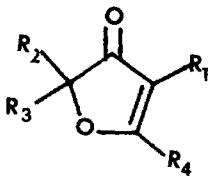
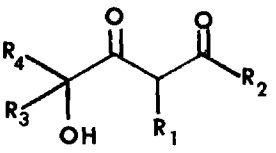
Summary: 2,2-Disubstituted 3(2H)-furanones can be prepared readily by 1,2-addition of organometallic compounds to γ,γ-disubstituted β-bromo-α,β-butenolides followed by treatment of the adducts with acid.

3(2H)-Furanones, which are valued for their aromas,[2] are useful synthetically as building blocks for muscarins[3] and tetronic acids[4] and as formyl ketone equivalents in photoannelation reactions.[5] Moreover, the findings that certain natural products such as jatrophone,[6] the eremantholides,[7] and geiparvarin[8] which exhibit anticancer activity contain a 3(2H)-furanone moiety have led to an increased interest in both the synthesis[9] and reactions[10] of these compounds.

Synthetic approaches to the 3(2H)-furanone system which vary in their degree of flexibility have appeared in the literature.[3,11] One of the general approaches to the synthesis of these compounds involves formation and acid-catalyzed cyclization of appropriate γ-hydroxy-β-dicarbonyl systems (2).[9,11c,d,g-j] It occurred to us that α,β-butenolides such as 4, having appropriate substituents at the β-carbon, should undergo 1,2-addition of organometallic reagents to yield masked γ-hydroxy-β-dicarbonyl compounds (3) which should be capable of undergoing hydrolysis and acid-catalyzed cyclization to the corresponding 3(2H)-furanones (1) possibly via intermediates such as 2.

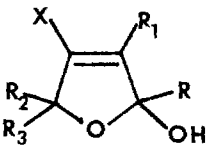


1

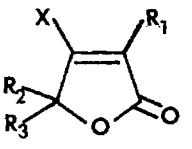


2

a. $R_1=R_2=R_3=R_4=CH_3$
b. $R_1=R_4=CH_3, R_3R_2=(CH_2)_5$
c. $R_1=H, R_2=R_3=CH_3, R_4=Ph$
d. $R_1=H, R_2=R_3=R_4=CH_3$
e. $R_1=H, R_2R_3=(CH_2)_5, R_4=CH_3$



3



4

a. $R_1=R_2=R_3=CH_3$, X=Br
b. $R_1=CH_3$, $R_2R_3=(CH_2)_5$, X=Br
c. $R_1=H$, $R_2=R_3=CH_3$, X=Br
d. $R_1=H$, $R_2R_3=(CH_2)_5$, X=Br
e. $R_1=CH_3$, $R_3=H$, $R_2=i$-Pr, X=Br

Various α,β-butenolides containing dialkylamino,[12] phenylthio,[13] or chloro[14] substituents at the β-position have been recently reported in the literature and appeared to be potentially useful candidates for the sesquence described above. However, we have found that lithium E-3-bromo-3-lithiopropenoate and its 2-methyl derivative, which can be obtained by treatment of the corresponding E-bromoacids with 2 equiv of n-butyllithium in ether or tetrahydrofuran at -70°C,[15] undergo facile addition to both aliphatic aldehydes and ketones[16] to give the corresponding γ-substituted β-bromobutenolides. Compounds 4a-e were prepared in yields in the 50-80% range by this method and their readily availability made them attractive precursors for the desired 3(2H)-furanones.

Benetti and coworkers have reported that β-alkyl substituted butenolides undergo 1,2-addition of 2 equiv. of Grignard or organolithium reagents to yield unsaturated 1,4-diols.[17] However, by carrying out inverse addition of phenyl- or methyllithium or methylmagnesium bromid to solutions of bromobutenolides 4a-e in ether at -25° it was possible to limit 1,2-addition tc only 1 equiv. of the organometallic reagent and obtain, after acidification, adducts of the typ 3. These adducts were not purified but were converted directly into 2,2-disubstituted furanones 1 by treatment with 20% aqueous sulfuric acid containing methanol as a cosolvent at room temperature for 14 h. The results of these runs are shown in the Table. The yields of products ranged from 47-76%. In the cases where relatively low yields were obtained, no improvement was observed when milder conditions applicable to the hydrolysis of vinyl halides[18] were employed.

The exact pathway for the conversions of the butenolide adducts 3 into the 3(2H)-furanones 1 is not known. An open chain γ-hydroxy-β-bromo-α,β-unsaturated ketone which may be in equilibrium with 3, may undergo hydrolysis of the vinyl halide to give a γ-hydroxy-β-dicarbonyl compound (2) which cyclizes to 1, or the hydroxyl group in 3 may undergo acid-catalyzed allylic rearrangement to the carbon atom bearing bromine followed by loss of hydroger bromide.

When the γ-isopropyl butenolide 4e was reacted with 1 equiv. of methyllithium and the product subjected to hydrolysis as described above, 3-bromo-2-isopropyl-5-methylfuran was the only product obtained.[19] Thus the above sequence appears to be applicable to the synthesis 2,2-disubstituted 3(2H)-furanones only. However, it does offer remarkable flexibility particularly with regard to the substituents which may be introduced at the 2 and 5 positions.

Table. Preparation of 2,2-Disubstituted 3(2H)-Furanones (1) by Addition of Organometallic Reagents to β-Bromobutenolides Followed by Acid Hydrolysis.

Butenolide	Organometallic Reagent	3(2H)-Furanone[a]	Yield (%)	Ref.
4a	CH_3Li	1a	56	-
4b	CH_3Li	1b	76	-
	CH_3MgI	1b	67	-
4c	PhLi	1c	71	4,20
	CH_3Li	1d	47	11i
4d	CH_3Li	1e	70	11j

a. All of the 3(2H)-furanones exhibited the expected UV, IR, NMR (^1H and ^{13}C), and mass spectral properties. All new compounds gave elemental analyses which were correct to within ±0.3%.

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15. The conversion of E-3-bromo-2-methylpropenoic acid into lithium E-3-bromo-3-lithio-2-methylpropenoate by treatment with 2 equiv. of t-butyllithium in THF at low temperature has been reported (Aberhart, D. J.; Tann, C.-H. J. Chem. Soc., Perkin I, 1979, 939).

16. Although several β-lithio propenoic acid derivatives having heteroatoms at the β-position having been prepared and reacted with certain carbonyl compounds,[12,13] no examples of additions of reagents of this type to aliphatic ketones have been reported.

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THE SYNTHESIS OF (±)-UMBELACTONE[1]

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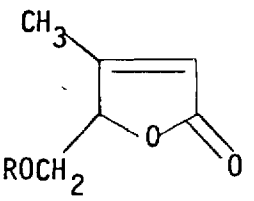
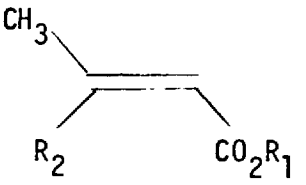
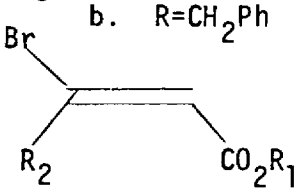
Numerous physicologically active compounds contain an α,β-butenolide system.[2] Umbelactone (1a) is an example of a naturally occurring γ-hydroxymethyl-α,β-butenolide which was isolated recently from Memycelon Umbelatum Burm.[3,4] The crude extract of this plant has been shown to exhibit activity against Ranikhe disease virus and also to have spasmolytic and antiamphetamine activity.[5]



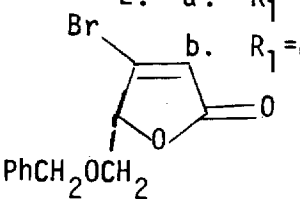
1 a. R=H
b. R=CH_2Ph



2. a. $R_1=R_2=Li$
b. $R_1=H$, $R_2=Br$



3 a. $R_1=R_2=Li$
b. $R_1=R_2=H$



4

We wish to report the first synthesis of (±)-1a via preparation of its benzyl derivative 1b followed by removal of the hydroxyl protecting group by catalytic hydrogenation. Two routes were employed for the synthesis of 1b. The first and shorter of these involved preparation of lithium Z-3-lithio-2-butenoate (2a) by treatment of the corresponding bromo acid 2b

with 2 equiv of n-butyllithuim in ether at -78°[6] and reaction of this organolithium reagent with benzyloxyacetaldehyde followed by acidification. The approach allowed the preparation of 1b in 61% yield and in a one-pot process, but it suffers from the disadvantage that the starting bromoacid 2b is not readily available. In fact, the best procedure which we have found for the preparation of 2b allowed its isolation in only about 10% yield. This involved the Favorskii rearrangement of a mixture of tribromobutanones to a mixture of 2b and the isomeric Z- and E-3-bromo-2-methylpropenoic acids and isolation of the desired product by crystallization.[6,7,8]

Recently, we found that β-bromo-α,β-butenolides may be prepared by reaction of lithium E-3-bromo-3-lithiopropenoates, e.g. 3a, with carbonyl compounds in tetrahydrofuran (THF) or diethyl ether at -78° followed by acidification.[9] It appeared that if the bromobutenolide 4 could be synthesized by this method that it should be possible to replace the halogen atom by a methyl group using a appropiate cuprate reagent.[10] This approach to butenolide 1b was also successful but we were able to accomplish the last step only in low yield.

The organolithium reagent 3a which was required for the synthesis of 4 was prepared by treatment of the corresponding E-bromo acid 3b with 2 equiv of n-butyllithium in THF at -78°. (E-Bromo acid 3b was easily prepared by heating a neat sample the corresponding Z-isomer,[11a] which is readily available from Favorskii rearrangement of tribromoacetone,[11b] at 120° for 3 h.). Reaction of 3a with benyzloxyacetaldehyde in THF -78° followed by acidification gave the β-bromobutenolide 4 in 65% yield. Treatment of this compound with the lithium dimethylcuprate-dimethyl sulfide complex[12] at -78° for 4 h, followed by warming of the mixture to -30°, workup under acidic conditions, and separation of the product from the unreacted β-bromobutenolide by preparative thin layer chromatography allowed the isolation of the desired β-methylbutenolide

1b in 28% yield (the yield was 55% based upon unrecovered starting material). Several attempts were made to improve the yield in the conversion of 4 into 1b using the lithium dimethylcuprate reagent. When the reaction was run at -30° rather than -78° a significant amount of what appeared to be the β,γ-double isomer of 4 was recovered. This suggested that at the higher temperature partial deprotonation of the butenolide by the cuprate reagent had occurred. When a longer reaction time or a larger excess of the cuprate reagent was employed a smaller quantity of starting material was recovered, but the isolated yield of 1b was not improved. Lithium methylthiophenylcuprate has been used successfully for the conversion of cyclic β-haloenones into the corresponding β-methyl enones.[13] However, attempts to use this reagent for the conversion of 4 into 1b were relatively unsuccessful.

Hydrogenolysis of the benzyl group in 1b in ethyl alcohol containing 10% palladium-on-carbon at atmospheric pressure gave crude (±)-umbelactone (1a) in ~90% yield. Subjection of the material to preparative TLC gave pure (±)-1a, mp 60-62°. The synthetic material showed identical IR and NMR (^{1}H and ^{13}C) spectral properties to an authentic sample of (+)-umbelactone.[14]

The mass spectra of the two samples were also the same within experimental limits on our instruments. However, on electron impact ionization a peak at m/e 129 (M + 1) was the highest mass peak and on chemical ionization a peak at m/e 257 corresponding to a protonated dimer structure was observed. Apparently, umbelactone has a very strong tendency to associate in the gas phase.[15] An isomer of 1a having the methyl group at the α rather than the β position exhibited the same kind of mass spectral behavior as that of 1a. We are currently investigating the mass spectral properties of other γ-hydroxymethylbutenolides.

Experimental Section[16]

Reaction of Lithium Z-3-Lithio-3-methylpropenoate (2a) with Benzyloxyacetaldehyde. To a solution of 1.65 g (10 mmol) of Z-3-bromo-3-methylpropenoic acid in 100 mL of anhydrous ether at -78° was added dropwise with stirring under nitrogen 18.00 mL (20 mmol) of 1.08 M n-butyllithium. The reaction mixture was stirred for 4 h at -78° and a solution of 1.50 g (10.00 mmol) of benzyloxyacetaldehyde in 10 mL anhydrous ether was added dropwise with stirring. The mixture was stirred for 3 h at -78° and allowed to warm to room temperature. Water (50 mL) was added and after the layers were separated the aqueous layer was acidified with 3N HCl and extracted with three 30-mL portions of ether. The combined ethereal extracts were washed with a saturated brine solution and dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo the crude sample was subjected to preparative TLC on silica gel plates with 1:1 ethyl acetate-hexane as the eluting solvent to yield 1.33 g (61%) of the butenolide 1b as a colorless oil: IR (CCl_4) 3060, 3020,2900, 2855, 1785, 1645, 1480, 1450, 1435, 1380, 1360, 1282, 1165, 1145, 1115, 1069, 937, 858, 845, 690 cm^{-1}; H NMR (CCl_4)δ2.18 (d, J=1 Hz, 3 H), 3.75 (d, J = 4 Hz, 2 H), 4.60 (m, 2 H), 4.82 (m, 1 H), 5.78 (m, 1 H), and 7.24 ppm (m, 5 H); mass spectrum:m/e (70 eV) M^+ 218.0980 (calcd 218.0943).

Reaction of lithium E-3-Bromo-3-lithiopropenoate (3a) with Benzyloxyacetaldehyde. To solution of 2.0 g (13.3 mmol) of E-3-bromopropenoic acid (3b) in 150 mL of anhydrous THF was added dropwise with stirring at -78° under nitrogen 18.0 mL (22.5 mmol) of 1.25 M n-butyllithium. The mixture was stirred for 4 h at -78° and a solution of 1.0 g (6.67 mmol) of benzyloxyacetaldehyde in 10 mL of dry THF was added dropwise via a syringe. The mixture was stirred for 3 h at -78° and then allowed to warm to room temperature. Water (50 ml) was added, the aqueous layer was separated, acidified with cold

3N HCl and extracted with three 20-mL portions of ether. The combined ethereal extracts were washed with two 20-mL portions of a saturated solution of $NaHCO_3$, two 20-ml portions of saturated brine, and dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo recrystallization of the residue from low boiling petroleum ether gave 1.23 g (65%) of butenolide 4 as off-white crystalls: mp 57.0-58.0°; IR (CCl_4) 3020, 2920, 2850, 1785 (broad), 1605, 1540, 1450, 1360, 1320, 1240, 1140, 1051, 1000, 920, and 850 cm^{-1}; ^1H NMR (CCl_4) δ 3.80 (d, J = 2 Hz, 1 H), 3.85 (d, J =2 Hz, 1 H) 4.52 (s, 2H), 4.94 (m, 1 H), 6.02 (d, 2 Hz, 1 H), 7.22 ppm (m, 5 H). Anal. Calcd. for $C_{12}H_{11}BrO_3$: C, 50.90; H 3.92. Found: C, 50.93; H, 3.93.

Conversion of β-Bromobutenolide 4 into the β-Methylbutenolide 1b by Reaction with $(CH_3)_2$ CuLi -$(CH_3)_2S$. A solution of methyllithium (3.20 mL of 1.7 M CH_3Li in ether) was added dropwise with stirring under nitrogen to a solution of 0.8 g (4 mmol) of $CuBr \cdot S(CH_3)_2$ in 5 mL each of $(CH_3)_2S$ and anhydrous ether at -20° until the initially formed yellow precipitate of CH_3Cu just dissolved. The resulting colorless solution was cooled to -78° and a solution 0.56 g (2.00 mmol) of butenolide 4 in 10 mL dry THF was added dropwise with stirring. The mixture was stirred at -78° for 4 h, allowed to warm to -30° and 1 mL of 2N HCl was added. Then, 20 mL of a saturated solution of NH_4Cl was added and the mixture was stirred vigorously for 15 min while being allowed to warm to room temperature. The mixture was filtered and the layers were separated. The organic layer was washed with a saturated brine solution and dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo the residue was subjected to preparative TLC on silica gel plates using 1:1 ethyl acetate : hexane as the developing solvent. This led to the recovery of 0.28 g of the starting butenolide 4 and 0.12 g (55% based upon unrecovered starting material) of the β-methylbutenolide 1b. The product showed identical spectral properties to those reported above.

Preparation of (±)-Umbelactone (1a). A stirred mixture of 100 mg of 5% palladium-on-carbon in 20 mL of absolute ethyl alcohol was presaturated with hydrogen. Then, 0.42 g of the butenolide 1b in 10 mL of absolute ethyl alcohol was added via a syringe. Hydrogenolysis of the mixture was carried out at 25° and 1 atm pressure until the theoretical amount of hydrogen (~40.00 ml) was absorbed. The catalyst was removed by filtration and the ethyl alcohol was removed in vacuo. The residue oil was dissolved in 50 mL of ether and the solution was dried over anhydrous magnesium sulfate. After removed of the solvent in vacuo the residue was subjected to preparative TLC on silica gel plate using a 4:1 hexane : ethyl alcohol mixture to give 0.19 g (76%) of (±)-umbelactone 1a; mp 60-62°.

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10. Larock and coworkers (Ref. 2c) have reported that certain organocuprates react readily with β-chloro-α,β-butenolides to give the corresponding β-alkyl derivatives. However, no specific examples were provided.

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14. We are grateful to Dr. R.P. Rastogi for providing us with an authentic sample of (+)-umbelactone.

15. In order to confirm that umbelactone exists as a monomer in the solid state an x-ray diffraction analysis was performed on a single crystal of (±)-umbelactone. We are grateful to Dr. Dan VanDever and Mr. Everett Crews for carrying out this analysis for us.

16. Melting points were determined with a Fisher-Johns hotstage and are uncorrected. The IR spectra were determined with a Perkin-Elmer 457 infrared spectrophotometer. The 'H NMR spectra were determined at 60 MHz with a Varian Model T-60 spectrometer or at 300 MHz with a Bruker Model WM-300 NMR spectrometer. The ^{13}C spectra were determined at 75 MHz with a Bruker Model WM-300 NMR spectrometer. The chemical shifts are expressed in δ values relative to Me_4Si as the internal standard. The mass spectra were obtained with either a Hitachi Perkin-Elmer Model RMU-7 or a Varian Mat Model 112S mass spectrometer. Microanalyses were performed by Atlantic Microlabs, Inc., Atlanta, GA.